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Clinical Protocol CA209451

A Randomized, Multicenter, Double-Blind, Phase 3 Study of Nivolumab, Nivolumab in Combination with Ipilimumab, or Placebo as Maintenance Therapy in Subjects with Extensive-Stage Disease Small Cell Lung Cancer (ED-SCLC) after Completion of Platinum-based First Line Chemotherapy

(CheckMate 451: CHECKpoint pathway and nivolumab clinical Trial Evaluation 451)

Revised Protocol Number: 06

Medical Monitor

Wen Hong Lin, MD

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 06	20-Sep-2018	• Moved OS of nivolumab vs placebo to secondary objectives • The associated power analysis was updated for the primary objective to reflect nivolumab in combination with ipilimumab vs placebo. Subsequently, number of events required for primary analysis of OS was changed from 593 to 386. • Added prohibited live / attenuated vaccine during treatment and until 100 days post last dose to prohibited and/or restricted treatments. • Updated study personnel
Revised Protocol 05	14-Jul-2018	• BICR-assessed PFS was changed as a primary objective to secondary objective and the associated interim analysis was removed • Tumor mutational burden (TMB) added as a potential predictive biomarker secondary objective • The number of events required for primary analysis of OS was changed from 576 events to 593 events • Study personnel was updated
Revised Protocol 04	19-Oct-2017	• Details of tissue requirements updated • Maximum treatment duration added • Contraception language updated to program standards • Exclusion criteria added botanical preparations • Prohibited/restricted treatments updated • Dose modifications were updated to program standards • Immune-mediated adverse events description added • RECIST 1.1 updated as per BMS standards
Revised Protocol 03	31-Aug-2016	Incorporates Amendment 11
Amendment 11	31-Aug-2016	Extended the time to randomization and modified tissue requirements for eligibility. The period following last dose of chemotherapy has been extended from 7 to 9 weeks (and from 9 to 11 weeks if patients undergo PCI). Updates based on nivolumab IB. Changed the requirement to collect amylase and lipase to amylase or lipase. Added amylase or lipase testing to follow up requirements. Clarified the exploratory objective to measure time to symptom deterioration includes the nivolumab monotherapy arm, the timing for PFS analysis was specified to be approximately around 6 months after last patient is randomized, dose modifications, criteria to resume treatment and discontinuation criteria were and safety algorithms were updated.
Revised Protocol 02	11-May-2016	Incorporates Amendment 10
Amendment 10	11-May-2016	Corrected typographical errors and update to match BMS protocol model document, provided time for males who are sexually active with a WOCBP to use contraception in section 3.3.1 number 3, removed language that IP cannot be destroyed from section 4.8, added a bullet to OS language in section 8.1 and removed - from section

Document	Date of Issue	Summary of Change
		8.4.5.2.
Revised Protocol 01	20-Apr-2016	Incorporates Amendment 09
Amendment 09	20-Apr-2016	[redacted]
Original Protocol	02-Jul-2015	Not applicable

OVERALL RATIONALE FOR REVISED PROTOCOL 06:

After removing the PFS as co-primary endpoint for the two treatment arms (vs placebo) in revised protocol 05, revised protocol 06 modifies the CA209451 endpoints in order to have OS of nivolumab plus ipilimumab vs placebo as the only primary endpoint. OS for nivolumab vs placebo will be tested hierarchically as a secondary endpoint, thus allowing for the use of the full 5% alpha on the OS for the nivolumab plus ipilimumab combination vs placebo.

At the time of study design, there were very limited data about immunotherapy in SCLC, mostly with single agent PD-1 inhibitors and less so with immunotherapy combinations of PD-1/CTLA4 inhibitors. Therefore, the rationale for removing OS from nivolumab monotherapy vs placebo as a co-primary endpoint in CA209451 is based on more mature data from the SCLC cohorts in CA209032 and from recently published data with immunotherapy in the SCLC maintenance setting.

Nivolumab plus ipilimumab showed, in fact, superior efficacy to nivolumab in the randomized SCLC cohorts in CA209032, with a statistically significant higher ORR.[1] Additionally, in a similar setting to the CA209451 study, pembrolizumab as a maintenance therapy showed a median OS of 9.6 months in patients with SCLC that did not progress after 1L chemotherapy in a single arm study.[2] This is not superior to the expected OS with observation only as per current standard of care, thus suggesting a potential for a more significant clinical benefit for the combination immunotherapy approach as compared to single agent. Additionally, the DMC has monitored the CA209451 study every 6 months and has not identified any safety signal in either the nivolumab plus ipilimumab arm or the nivolumab arm.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 06

Section Number & Title	Description of Change	Brief Rationale
Synopsis, Section 1.3.1 Primary Objectives Section 1.3.2 Secondary Objectives Figure 3.1-1 Schema Section 5.4.2 Primary and Secondary Efficacy Assessments Section 8.3.2 Secondary Endpoints Section 8.4.2 Efficacy Analyses	OS of nivolumab vs placebo moved to secondary objective	Data from the SCLC cohorts with immunotherapy in the SCLC setting supports change in study design.
Synopsis Section 8.1 Sample Size Determination	The associated power analysis was updated for the primary objective to reflect nivolumab in combination with ipilimumab vs placebo. Subsequently, number of events required for primary analysis of OS was changed from 593 to 386.	New power analysis implemented for updated primary objective.
Section 3.4.1 Prohibited and/or Restricted Treatments	Added prohibited live / attenuated vaccine during treatment and until 100 days post last dose to prohibited and/or restricted treatments.	Align with nivolumab program standards for safety

[redacted]

SYNOPSIS

Clinical Protocol CA209451

Protocol Title: A Randomized, Multicenter, Double-Blind, Phase 3 Study of Nivolumab, Nivolumab in Combination with Ipilimumab, or Placebo as Maintenance Therapy in Subjects with Extensive-Stage Disease Small Cell Lung Cancer (ED-SCLC) after Completion of Platinum-based First Line Chemotherapy

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s):

This is a randomized, double-blind, three-arm, multicenter, Phase 3 study in adult subjects with ED-SCLC, who achieve Stable Disease, Partial Response or Complete Response after completion of platinum based first line chemotherapy.

Approximately 810 subjects will be randomized in a 1:1:1 ratio to treatment with either nivolumab monotherapy (Arm A), nivolumab/ipilimumab combination therapy (Arm B), or placebo (Arm C), and will be stratified according to the following factors:

- ECOG Performance Status: 0 vs 1
- Gender: Male vs Female
- Prophylactic Cranial Irradiation (PCI) following chemotherapy: Yes vs No

The treatment arms are as follows:

Arm A:

Nivolumab 240 mg administered every 2 weeks as a 30 min IV infusion

Arm B:

Nivolumab 1 mg/kg (30 min IV infusion) and ipilimumab 3 mg/kg (90 minute IV infusion) every 3 weeks for four doses, followed by nivolumab 240 mg every 2 weeks.

Arm C:

Placebo

In order to maintain a blinded study, the schedule of investigational and placebo treatments is divided into two 6-week cycles at the start of therapy, followed by ongoing 2-week cycles until discontinuation criteria are met.

On-study tumor assessments will be conducted every 6 weeks (± 5 days) for the first 36 weeks. After Week 36, tumor assessments will be performed every 12 weeks (± 5 days) until disease progression

Duration of the study from start of randomization to analysis of the primary endpoint will be approximately 35 months (28 months of accrual + 7 months of minimum follow-up, providing an average follow up of 9 months). Additional survival follow-up may continue for up to 5 years from the primary analysis of survival. The study will end once survival follow-up has concluded.

Study Phase: III

Research Hypothesis:

Maintenance treatment with nivolumab monotherapy, or nivolumab in combination with ipilimumab followed by nivolumab monotherapy, will prolong overall survival (OS) as compared with placebo in subjects with ED-SCLC who have completed platinum-based first line chemotherapy.

Objectives:

Primary Objectives:

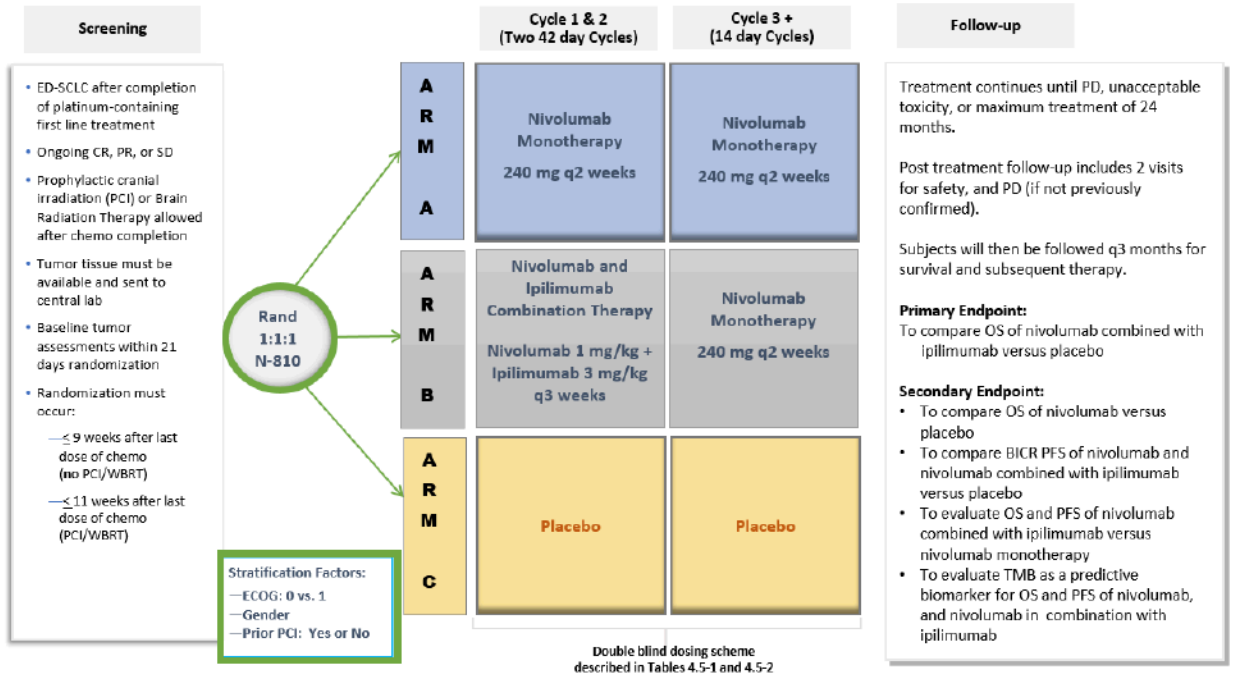
To compare OS of nivolumab in combination with ipilimumab versus placebo in subjects with ED-SCLC after completion of platinum-based first line chemotherapy.

Secondary Objectives:

- To compare OS of nivolumab versus placebo in subjects with ED-SCLC after completion of platinum-based first line chemotherapy
- To compare Blinded Independent Central Review (BICR) assessed PFS of nivolumab, and nivolumab in combination with ipilimumab versus placebo
- To evaluate (descriptively) OS and BICR-assessed PFS of nivolumab combined with ipilimumab versus nivolumab monotherapy.
- To evaluate tumor mutational burden as a predictive biomarker for OS and PFS of nivolumab, and nivolumab in combination with ipilimumab

[redacted]

Study Design:



Study Population:

Key Inclusion Criteria

1) Subjects with SCLC documented by histology or cytology from brushing, washing or needle aspiration of a defined lesion, but not from sputum cytology alone.
2) Subjects must have presented at initial diagnosis with extensive stage disease (defined as Stage IV (T any, N any, M1a/b) per NCCN guidelines Version 1.2015, AJCC Cancer Staging Manual, 7th Edition, 2010).
3) Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1. (See Appendix 1)
4) Subjects must have received 4 cycles of platinum-based first line chemotherapy and must have an ongoing response of complete response (CR), partial response (PR), or stable disease (SD) after completion of chemotherapy. Acceptable combinations, as recommended per NCCN guidelines, include cisplatin or carboplatin combined with either etoposide or irinotecan.
   a) As an exception to the above criterion, subjects receiving only 3 cycles of chemotherapy due to toxicity are eligible, if they have an ongoing PR or CR after the 3rd cycle.
   b) Subjects who have received > 4 cycles of platinum-based first line chemotherapy are not eligible
5) Subjects must be randomized ≤ 9 weeks (63 days), from the last dose of platinum-based first line chemotherapy. Subjects receiving PCI or brain RT must be randomized ≤ 11 weeks (77 days) of the last dose of platinum-based first line chemotherapy.
   a) Study therapy must not be administered < 3 weeks (21 days) from the last dose of platinum-based first line chemotherapy.
   b) Blinded study therapy must not be administered < 2 weeks (14 days) from the last dose of radiotherapy.
6) A formalin-fixed, paraffin-embedded (FFPE) tumor tissue block (preferred) or 10 unstained slides of tumor sample (archival or recent) for biomarker evaluation must be available and submitted to the central lab for correlative studies in order for a subject to be randomized. If fewer than 10 slides are available, the BMS Medical Monitor or Study Director may approve randomization of subject upon review of the case. Specimens must have been submitted to the central laboratory prior to randomization. Excisional, incisional or core needle biopsies are strongly preferred, however samples collected via endobronchial ultrasound (EBUS) guided biopsy

(using a 22g needle or larger) and transbronchial lung biopsy (TBLB) are acceptable. In certain cases, the BMS Medical Monitor or Study Director may approve submission of samples collected via other methods.

Study Drug: includes both Investigational [Medicinal] Products (IP/IMP) and Non-investigational [Medicinal] Products (Non-IP/Non-IMP) as listed:

Study Drug for BMS-936558		
Medication	**Potency**	**IP/Non-IP**
Nivolumab Solution for Injection	100 mg (10 mg/mL)	IP
Ipilimumab Solution for Injection	200 mg (5 mg/mL)	IP
0.9% Sodium Chloride for Injection	N/A	IP
5% Dextrose for Injection	N/A	IP

Study Assessments:

Safety assessments include AEs, physical examinations, vital signs, ECOG performance status, assessment of signs and symptoms, laboratory tests, pregnancy tests.

Some of the previously referred to assessments may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations

Statistical Considerations:

Sample Size: Approximately 810 subjects will be randomized to three treatment arms in a 1:1:1 ratio. The primary objective is to compare OS of nivolumab in combination with ipilimumab versus placebo.

The analysis of primary endpoint of OS will be conducted when at least 386 deaths have been observed pooled across the nivolumab in combination with ipilimumab and the placebo treatment groups. It is expected that 208 events will be observed in placebo and 178 in the experimental arm. With 386 events available for comparison of OS in nivolumab in combination with ipilimumab treatment group vs placebo, power of the log-rank test is approximately 90% to detect a hazard ratio (HR) of 0.72 with a type I error of 0.05 (two-sided). Power calculations were performed using EAST® Software. For nivolumab in combination with ipilimumab, a 3months delay effect versus placebo and an HR of 0.68 post delay was assumed, resulting into an overall HR (experimental vs placebo) of 0.72 at time of the OS analysis. Survival function for placebo arm was modeled using a four hazard pieces to match historical data. Median OS derived from the survival functions were 8.8 and 11.0 months for the placebo and experimental arms, respectively.

Given the observed accrual, it is expected that the duration of the study from start of randomization to analysis of primary endpoint will be approximately 35 months (28 months of accrual + 7 months of follow-up, providing an average follow up of 9 months).

The independent Data Monitoring Committee (DMC) will have access to periodic interim safety and efficacy reports to allow for a risk/benefit assessment.

Analyses: The OS analyses will be conducted using a two-sided log-rank test stratified by the stratification factors in all randomized subjects to compare each of the two experimental treatments to the control group. Hierarchical procedure will be used to control the overall Type I error rate at 0.05. The secondary endpoint, OS comparing nivolumab monotherapy vs placebo, will be tested using 2-sided 5% alpha, if superiority of nivolumab in combination with ipilimumab over placebo is demonstrated at the 5% significance level. HRs and corresponding two-sided CIs will be estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by the above factors. OS curves, OS medians with 95% CIs, and OS rates at 6, 12, and 18 months with 95% CIs will be estimated using Kaplan-Meier methodology.

PFS secondary analyses will be conducted using all randomized subjects. HRs and corresponding two-sided CIs will be estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by the same stratification factors as above. PFS curves, PFS medians with 95% CIs, and PFS rates at 6, 12, and 18 months with 95% CIs will be estimated for each of the three treatment groups using Kaplan-Meier methodology.

[redacted]

Descriptive analyses of OS, PFS, and ORR will be performed to evaluate differences between the two experimental arms, nivolumab combined with ipilimumab and nivolumab monotherapy. These include HRs and medians with corresponding two-sided 95% CIs for OS and PFS, as well as an ORR odds ratio with corresponding 95% CI.

Descriptive analyses will be performed to evaluate the potential of PD-L1 expression and TMB as a predictive biomarker for efficacy.

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[redacted]

1.2 Research Hypothesis

Maintenance treatment with nivolumab monotherapy, or nivolumab in combination with ipilimumab followed by nivolumab monotherapy, will prolong overall survival (OS) as compared with placebo in subjects with ED-SCLC who have completed platinum-based first line chemotherapy.

1.3 Objectives(s)

1.3.1 Primary Objectives

To compare OS of nivolumab in combination with ipilimumab versus placebo in subjects with ED-SCLC after completion of platinum-based first line chemotherapy.

1.3.2 Secondary Objectives

- To compare OS of nivolumab versus placebo in subjects with ED-SCLC after completion of platinum-based first line chemotherapy.
- To compare Blinded Independent Central Review (BICR) assessed PFS of nivolumab, and nivolumab in combination with ipilimumab versus placebo
- To evaluate (descriptively) OS and BICR-assessed PFS of nivolumab combined with ipilimumab versus nivolumab monotherapy.
- To evaluate tumor mutational burden as a predictive biomarker for OS and PFS of nivolumab, and nivolumab in combination with ipilimumab

1.3.3 [redacted]

[redacted]

1.4 Product Development Background

Nivolumab is in clinical development for the treatment of subjects with NSCLC, RCC, glioblastoma and other cancer types. Recently, nivolumab was approved by the FDA for the treatment of patients with advanced squamous NSCLC and melanoma. Nivolumab is also approved for the treatment of advanced melanoma in Europe, Japan, and other countries.

In the Phase 1/2 trial, CA209032, in subjects with heavily pretreated SCLC, nivolumab monotherapy showed an ORR of 18%, while the combination of nivolumab and ipilimumab demonstrated an ORR of 30% in an updated analysis.[34] Study CA209451 will be the second Phase 3 study in the clinical development program for nivolumab in SCLC and will evaluate the efficacy and safety of nivolumab monotherapy and nivolumab and ipilimumab combination therapy, as maintenance treatment following first line platinum-based chemotherapy in subjects with ED-SCLC.

1.5 Overall Risk/Benefit Assessment

ED-SCLC is a disease with high unmet medical need. Despite a robust initial response rate to first line platinum-containing chemotherapy regimens, subsequent progression is typically rapid and overall survival rates are poor. Further, there are currently no agents approved in the maintenance setting for patients who respond to first line therapy. The clinical activity of nivolumab monotherapy, as well as nivolumab and ipilimumab combination therapy, observed in the CA209032 study suggests the potential for improved clinical outcomes relative to the current standard practice of observation and best supportive care.

Nivolumab, both as monotherapy and in combination with ipilimumab, can cause clinically relevant AEs, including liver toxicities, thyroiditis, pneumonitis, and diarrhea. However, these

toxicities are typically manageable or reversible with the Management Algorithms provided in Appendix 2 and the nivolumab IB.

To assure an ongoing favorable benefit-risk assessment for subjects enrolled onto CA209451, an independent Data Monitoring Committee (DMC) will be utilized to monitor the safety and efficacy of nivolumab versus nivolumab and ipilimumab versus placebo throughout the conduct of the trial.

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) and applicable local requirements.

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

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

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 study 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

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 (as per country guidelines) 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 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 a randomized, double-blind, three-arm, multicenter, Phase 3 study in adult subjects with ED-SCLC, who achieve Stable Disease, Partial Response or Complete Response after completion of platinum based first line chemotherapy.

Approximately 810 subjects will be randomized in a 1:1:1 ratio to treatment with either nivolumab monotherapy (Arm A), nivolumab/ipilimumab combination therapy (Arm B), or placebo (Arm C), and will be stratified according to the following factors:

- ECOG Performance Status: 0 vs 1
- Gender: Male vs Female
- Prophylactic Cranial Irradiation (PCI) following chemotherapy: Yes vs No

The treatment arms are as follows:

- **Arm A:**

Nivolumab 240 mg administered every 2 weeks as a 30 min IV infusion, as described in Table 4.5-1 and Table 4.5-2

- **Arm B:**
  - Nivolumab 1 mg/kg (30 min IV infusion) and ipilimumab 3 mg/kg (90 minute IV infusion) every 3 weeks for four doses, followed by nivolumab 240 mg every 2 weeks, as described in Table 4.5-1 and Table 4.5-2
- **Arm C:**
  - Placebo administered as described in Table 4.5-1 and Table 4.5-2

In order to maintain a blinded study, the schedule of investigational and placebo treatments is divided into two 6-week cycles at the start of therapy, followed by ongoing 2-week cycles until discontinuation criteria are met (Section 4.5.3.4). This schedule is described in Table 4.5-1 and Table 4.5-2.

On-study tumor assessments will be conducted every 6 weeks (± 5 days) for the first 36 weeks. After Week 36, tumor assessments will be performed every 12 weeks (± 5 days) until disease progression (Section 5.4).

Duration of the study from start of randomization to analysis of the primary endpoint will be approximately 37 months (28 months of accrual + 9 months of follow-up).

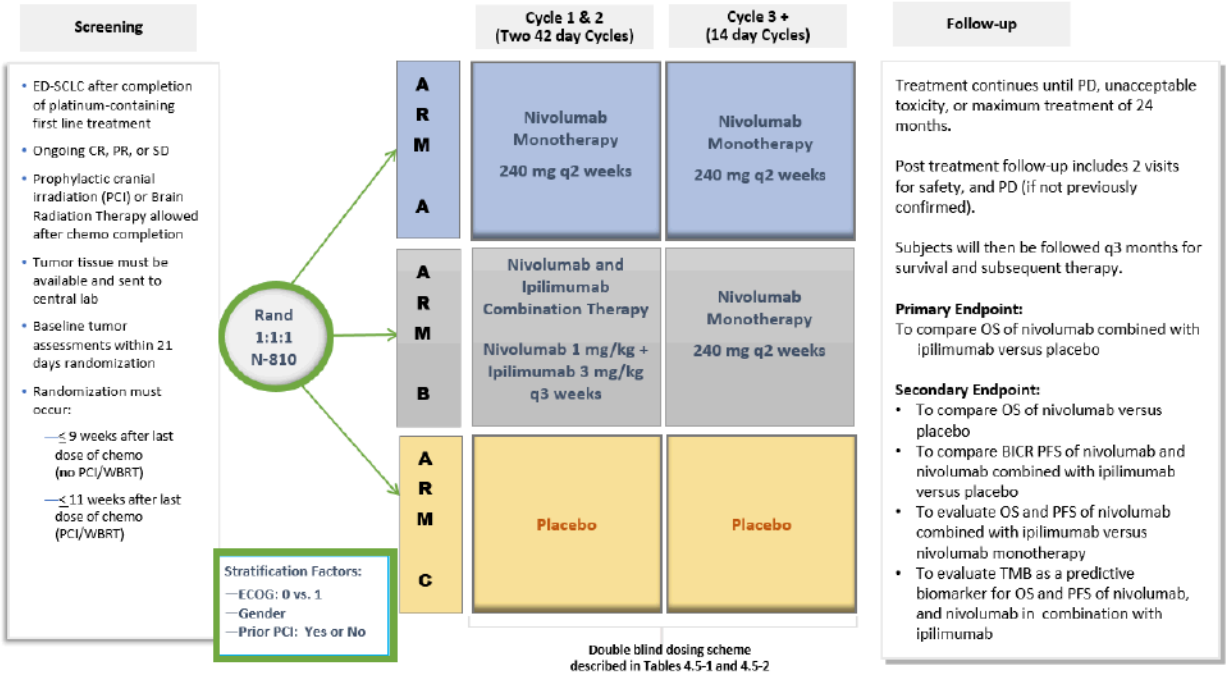
Additional survival follow-up may continue for up to 5 years from the primary analysis of survival. The study will end once survival follow-up has concluded.

The subjects safety will be monitored on an ongoing basis as described fully in Section 5.3. In addition, a BMS Medical Safety Team (MST) routinely reviews safety signals across the nivolumab program.

A Data Monitoring Committee (DMC) will be implemented to provide safety and overall risk/benefit monitoring of the study (Section 7).

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

Figure 3.1-1: Study Design Schematic



The start of the trial is defined as first visit for the first subject screened. The end of trial is defined as the last visit for the last subject. Study completion is defined as the final date on which data for the primary endpoint was collected.

3.1.1 Study Phases

The study is divided into the following phases: Screening, Treatment, and Follow-up.

3.1.1.1 Screening

- Screening begins after the subject signs the informed consent form (ICF)
- The subject is enrolled using the Interactive Voice Response System (IVRS)
- Tumor tissue must be available and submitted to the central lab for correlative studies in order for a subject to be randomized (except as described in Inclusion Criteria 2f). Subjects must

consent to allow the acquisition of tumor tissue by study personnel for performance of the correlative studies

- Baseline assessments must be performed within the timeframes described in Table 5.1-1:
- Prophylactic Cranial Irradiation (PCI) may be offered to subjects following the completion of first-line chemotherapy, per local standard of care
- For patients with known brain metastases, brain radiotherapy (Whole Brain Radiation Therapy (WBRT) or stereotactic radiation) may be offered , per local standard of care
- Brain radiotherapy (including PCI) must be completed ≥ 2 weeks prior to the start of blinded study therapy
- Subjects with incidental asymptomatic brain metastasis findings at screening are eligible only if, according to the clinical judgment of the investigator, these findings are unlikely to represent progression of disease after chemotherapy.
- Randomization must be performed ≤ 9 weeks from the last dose of chemotherapy for subjects not receiving brain radiotherapy (including PCI) and ≤ 11 weeks from the last dose of chemotherapy for subjects receiving brain radiotherapy (including PCI)
  - Blinded study therapy must not be administered < 3 weeks (21 days) from the last dose of platinum-based first line chemotherapy.
- The screening phase either ends with confirmation of full eligibility and randomization of the subject or with the confirmation that the subject is a screen failure
- This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure prior to randomization. If re-enrolled, the subject must be re-consented. A new subject identification number will be assigned by IVRS at the time of re-enrollment.

3.1.1.2 Treatment

- The treatment phase begins with the randomization call to the IVRS. The subject is randomly assigned to one of the 3 treatment arms. Treatment is to begin within 3 business days of randomization
- Blinded study therapy is administered as described in Table 4.5-1 until disease progression, discontinuation due to toxicity, withdrawal of consent, the study ends, or other criteria for discontinuation are met as described in Section 3.5 and 4.5.3.4. Subjects may be treated beyond initial progression as specified in Section 5.4
- Subjects will be evaluated for response according to RECIST 1.1 criteria. Radiographic assessments will be obtained in all treatment arms every 6 weeks for the first 36 weeks, and subsequently every 12 weeks, or more frequently as clinically indicated, until disease progression (or until discontinuation of blinded study drug in patients treated beyond progression) or withdrawal of study consent
- The Treatment phase ends when the subject is discontinued from blinded study drug(s)

Study assessments are to be collected as outlined in Table 5.1-2 and Table 5.1-3.

3.1.1.3 Follow-up

- Begins when the decision to discontinue a subject from blinded study therapy is made (no further treatment with blinded study drug(s))
- Subjects who discontinue blinded study therapy for reasons other than disease progression will continue to have radiographic assessments every 6 weeks (± 5 days) for the first 36 weeks after randomization, and subsequently every 12 weeks, until disease progression or withdrawal of study consent
- Follow up visits occur as follows:
  - X01 Follow up Visit 1 = 35 days ± 7 days from last dose,
  - X02 Follow up Visit 2 = 80 days ± 7 days from X01 Follow Up Visit 1
  - Survival Follow Up visits begin after the X02 Follow Up Visit 2:
    - For Survival Follow Up Visits, for all subjects, contact will be made (in person or by telephone) every 12 weeks upon entry into this phase to evaluate Overall Survival and collect data on the initiation of subsequent therapy for the treatment of SCLC

Study assessments are to be collected as outlined in Table 5.1-4.

3.2 Post Study Access to Therapy

At the conclusion of the study, subjects assigned to active study drug who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study drug for the maximum of 24 months including time on-study treatment. Study drug will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of BMS. BMS reserves the right to terminate access to BMS supplied study drug if any of the following occur: a) the marketing application is rejected by responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a government sponsored or private health program; or d) therapeutic alternatives become available in the local market.

3.3 Study Population

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

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

a) Subjects must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal subject care

b) Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests and other requirements of the study

2. Target Population

a) Subjects with SCLC documented by histology or cytology from brushing, washing or needle aspiration of a defined lesion, but not from sputum cytology alone

b) Subjects must have presented at initial diagnosis with extensive stage disease (defined as Stage IV (T any, N any, M1a/b) per NCCN guidelines Version 1.2015, AJCC Cancer Staging Manual, 7th Edition, 2010)

c) Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1 (See Appendix 1)

d) Subjects must have received 4 cycles of platinum-based first line chemotherapy and must have an ongoing response of complete response (CR), partial response (PR), or stable disease (SD) after completion of chemotherapy. Acceptable combinations, as recommended per NCCN guidelines, include cisplatin or carboplatin combined with either etoposide or irinotecan

   i) As an exception to the above criterion, subjects receiving only 3 cycles of chemotherapy due to toxicity are eligible, if they have an ongoing PR or CR after the 3rd cycle

   ii) Subjects who have received > 4 cycles of platinum-based first line chemotherapy are not eligible

e) Subjects must be randomized ≤ 9 weeks (63 days), from the last dose of platinum-based first line chemotherapy. Subjects receiving PCI or Brain RT must be randomized ≤ 11 weeks (77 days) from the last dose of platinum-based first line chemotherapy

   i) Blinded study therapy must not be administered < 3 weeks (21 days) from the last dose of platinum-based first line chemotherapy

   ii) Blinded study therapy must not be administered < 2 weeks (14 days) from the last dose of radiotherapy

f) A formalin-fixed, paraffin-embedded (FFPE) tumor tissue block (preferred) or 10 unstained slides of tumor sample (archival or recent) for biomarker evaluation must be available and submitted to the central lab for correlative studies in order for a subject to be randomized. If fewer than 10 slides are available, the BMS Medical Monitor or Study Director may still approve randomization of subjects upon review of the case. Specimens must have been submitted to the central laboratory prior to randomization. Excisional, incisional or core needle biopsies are strongly preferred, however samples collected via endobronchial ultrasound (EBUS) guided biopsy (using a 22g needle or larger) and transbronchial lung biopsy (TBLB) are acceptable. In certain cases, the BMS Medical Monitor or Study Director may approve submission of samples collected via other methods.

g) 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

3. Age and Reproductive Status

a) Men and women ≥ 18 years of age or age of majority inclusive.

b) Women of childbearing potential (WOCBP) must have 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 blinded study drug

c) Women must not be breastfeeding

d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with blinded study drug (s) plus the time required for the investigational drug to undergo approximately five half-lives plus 30 days (duration of ovulatory cycle) for a total of 5 months post-treatment completion

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with blinded study drug (s) plus the time required for the investigational drug to undergo approximately five half-lives plus 90 days (duration of sperm turnover) for a total of 7 months post-treatment completion

f) Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However they must still undergo pregnancy testing as described in this section

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise on the use of highly effective methods of contraception which have a failure rate of < 1% when used consistently and correctly.

a) Males, ages 18 or age of majority, inclusive

b) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug(s) blinded study therapy plus the time required for the investigational drug to undergo approximately five half-lives plus 90 days (duration of sperm turnover) for a total of 7 months post-treatment completion.

c) Azoospermic males are exempt from contraceptive requirements.

d) Male subjects must be willing to refrain from sperm donation during the entire study and for the time required for the investigational drug to undergo approximately7 months after the end of study treatment.

Investigators shall counsel male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.

At a minimum, subjects must agree to the use of one highly effective method of contraception as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. WOCBP and female partners of male subjects, who are WOCBP, are expected to use one of the highly effective methods of contraception listed below. Male subjects must inform their

female partners who are WOCBP of the contraceptive requirements of the protocol and are expected to adhere to using contraception with their partner. Contraception methods are as follows:

Highly Effective Contraceptive Methods That Are User Dependent
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[a] – oral – intravaginal – transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation[a] – oral – injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation a • Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and intrauterine hormone-releasing system (IUS)b • Intrauterine device (IUD)b • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence

NOTES:

[a] Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.

[b] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Unacceptable Methods of Contraception*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously
• Diaphragm with spermicide
• Cervical cap with spermicide
• Vaginal Sponge with spermicide
• Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus interruptus).
• Spermicide only
• Lactation amenorrhea method (LAM)

* Local laws and regulations may require use of alternative and/or additional contraception methods.

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Symptomatic CNS metastases are excluded. Subjects with previous brain metastases are eligible provided that they are asymptomatic, do not require treatment with radiation therapy, steroids or anticonvulsants, and have stable disease at the screening tumor assessment. In addition, subjects must have been either off corticosteroids, or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent). Blinded study therapy must not be administered < 2 weeks (14 days) from the last dose of radiotherapy

b) Subjects receiving consolidative chest radiation are excluded.

c) Carcinomatous meningitis

d) Pleural effusion which cannot be controlled with appropriate interventions

e) All toxicities attributed to prior anti-cancer therapy must have been resolved to Grade 1 (NCI CTCAE Version 4) or baseline before administration of blinded study drug(s) other than:

   i) Subjects with toxicities attributed to prior anti-cancer therapy that either are not expected to resolve and/or result in long lasting sequelae, such as neuropathy after platinum based therapy, or are not expected to interfere with treatment on study, such as fatigue or alopecia, are eligible

   ii) Subjects with grade 2 anemia, however hemoglobin level must be ≥ 8.0 g/dL

2. Medical History and Concurrent Diseases

a) Women who are pregnant or breastfeeding

b) Active, known or suspected autoimmune disease. Subjects with an autoimmune paraneoplastic syndrome requiring concurrent immunosuppressive treatment are excluded. Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll

c) A condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Corticosteroids with minimal systemic absorption (inhaled or topical steroids), and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease

d) Prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T cell co-stimulation or checkpoint pathways)

e) Interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity

f) Previous malignancies (except non-melanoma skin cancers, and the following in situ cancers: bladder, gastric, colon, endometrial, cervical/dysplasia, melanoma, or breast) unless a complete remission was achieved at least 2 years prior to study entry AND no additional therapy is required during the study period

g) Known medical condition that, in the investigator's opinion, would increase the risk associated with study participation or blinded study drug(s) administration or interfere with the interpretation of safety results

h) Major surgery or significant traumatic injury that is not recovered at least 14 days before the first dose of blinded study drug(s)

3. Physical and Laboratory Test Findings

a) Positive test for hepatitis B virus (HBV) using HBV surface antigen (HBVsAg) test or positive test for hepatitis C virus (HCV) using HCV ribonucleic acid (RNA) or HCV antibody test indicating acute or chronic infection

   i) Subjects with a positive test for HCV antibody but no detection of HCV RNA indicating no current infection are eligible

b) Known medical history of testing positive for human immunodeficiency virus (HIV) or known medical history of acquired immunodeficiency syndrome (AIDS).

c) Inadequate hematologic function defined by:

   i) Absolute neutrophil count (ANC) < 1,000/mm3·

   ii) Platelet count < 100,000/mm^3, or

   iii) Hemoglobin level < 8.0 g/dL

d) Inadequate hepatic function as defined by either:

   i) Total bilirubin level ≥ 1.5 times the ULN (except subjects with Gilbert's Syndrome, who are excluded if total bilirubin ≥ 3 times ULN), or

   ii) AST and ALT levels ≥ 2.5 times the ULN or ≥ 5 times the ULN if liver metastases are present

e) Inadequate pancreatic function as defined by either:

   i) Lipase > 1.5 ULN. Subjects with lipase > 1.5 ULN may enroll if there are neither clinical nor radiographic signs of a pancreatitis, OR

   ii) Amylase > 1.5 ULN. Subjects with amylase > 1.5 ULN may enroll if there are neither clinical nor radiographic signs of a pancreatitis

4. Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to any of the study drugs or study drug components

5. 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

c) Treatment with botanical preparations (eg, herbal supplements or traditional Chinese medicines derived from plants, minerals, or animals) intended for general health support or to treat the disease under study within 2 weeks prior to randomization/treatment

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

3.3.3 Women of Childbearing Potential

A 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) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40mIU/mL to confirm menopause.

*Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal:

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Postmenopausal women may continue HRT after FSH testing is completed and postmenopausal status is confirmed.

Other parenteral products may require washout periods as long as 6 months.

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

The following medications are prohibited during the study:

- Immunosuppressive agents (except to treat a drug-related AE or an autoimmune paraneoplastic syndrome). Subjects with an autoimmune paraneoplastic syndrome at enrollment requiring concurrent immunosuppressive treatment are not eligible.
- Thymosin, thymalfasin, and thymopentin are prohibited
- Systemic corticosteroids > 10 mg daily prednisone equivalent, except as stated in Section 3.4.3 or to treat a drug-related AE
- Any concurrent systemic antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, standard or investigational agents for the treatment of cancer).
- Surgical resection of tumor
- Any botanical preparations (eg herbal supplements or traditional Chinese medicines derived from plants, minerals, or animals) intended to treat the disease under study or provide supportive care
- Note: the following radiotherapy is permitted
  - Palliative bone radiotherapy as described in section 3.4.2
  - Palliative radiotherapy to a single metastatic site, other than bone, in subjects who do not require immediate initiation of second line systemic anti-cancer therapy. See Section 3.4.2 for additional restrictions.
- Any live / attenuated vaccine (eg varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella (MMR)) during treatment and until 100 days post last dose.

3.4.2 Other Restrictions and Precautions

Blinded study therapy must be resumed ≤ 6 weeks from the last dose or the subject must be permanently discontinued from blinded study therapy. (See exceptions in Sections 3.5 and 4.5.3.4 Discontinuation Criteria)

Non-target bone lesions that do not include lung tissue in the planned radiation field may receive palliative radiotherapy at any time while on study treatment. Radiotherapy to non-bone lesions is permitted only as described in Section 3.4.1. Study treatment must be withheld during radiotherapy and for two weeks after completion of radiotherapy. Details of palliative radiotherapy should be documented in the source records and case report form (CRF). Details in the source records should include: dates of treatment, anatomical site, dose administered and fractionation schedule, and AEs.

Subjects requiring palliative radiotherapy should be carefully assessed for disease progression. Subjects considered as having progressive disease are required to discontinue blinded study therapy, unless eligible to continue treatment beyond progression per the guidance in Section 5.4 (Treatment Beyond Disease Progression).

3.4.2.1 Imaging Restrictions and Precautions

It is the local imaging facility's responsibility to determine, based on subject attributes (eg, allergy history, diabetic history and renal status), the appropriate imaging modality and contrast regimen for each subject. Imaging contraindications and contrast risks should be considered in this assessment. Subjects with renal insufficiency should be assessed as to whether or not they should receive contrast and if so, what type and dose of contrast is appropriate. Specific to MRI, subjects with severe renal insufficiency (ie, estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this subject population. In addition, subjects are excluded from MRI if they have tattoos, metallic implants, pacemakers, etc.

The ultimate decision to perform MRI in an individual subject in this study rests with the site radiologist, the investigator and the standard set by the local Ethics Committee.

3.4.3 Permitted Therapy

Subjects are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses including doses > 10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

Postmenopausal women may continue HRT after FSH testing is completed and postmenopausal status is confirmed.

Concomitant palliative and supportive care for disease-related symptoms (including bisphosphonates and RANK-L inhibitors) are allowed. See Section 3.4.2 for guidance on concomitant palliative radiotherapy

3.5 Discontinuation of Subjects following any Treatment with Study Drug(s)

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

- Disease progression as assessed by RECIST 1.1 criteria (Appendix 3), unless the subject meets criteria for treatment beyond progression (Section 5.4)
- Subject's request to stop study treatment
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Termination of the study by Bristol-Myers Squibb (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
- Unblinding a subject for any reason (emergency or non-emergency)
- Additional protocol-specified reasons for discontinuation, as described in Section 4.5.3.4

In the case of pregnancy, the investigator must immediately notify the Sponsor or designee of this event. In most cases, the blinded study drug(s) will be permanently discontinued in an appropriate manner. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of blinded study drug(s), a discussion between the investigator and the Sponsor or designee must occur.

All subjects who discontinue blinded study drug(s) 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).

Subjects must be followed for at least 100 days after the last dose of blinded study therapy. Follow-up (FU1) occurs approximately 35 days (+/- 7 days) after last dose of coinciding with the date of discontinuation (+/- 7 days) if the date of discontinuation is greater than 35 days after the last dose. Follow up visit 2 (FU2) occurs approximately 80 days (+/- 7 days) after FU1. Survival visits are every 3 months from FU2 up to 5 years and may be conducted during a clinic visit or via the phone. The endpoint of this study is OS, and so tracking reporting the subject's status in the follow up setting according to the protocol guidelines for disease progression and survival are critical to the final study analysis. The importance of follow up should be clearly communicated to study subjects.

If blinded study drug(s) 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 and entered on the appropriate case report form (CRF) page.

3.6 Post Study Drug Study Follow up

In this study, overall survival is a key endpoint of the study. Post study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study drug must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

BMS may request that survival data be collected on all randomized subjects outside of the protocol defined window (See Table 5.1-4). 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.

3.6.1 Withdrawal of Consent

Subjects who request to discontinue blinded study therapy will remain in the study and must continue to be followed for protocol specified follow-up procedures. 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**, if possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with blinded study therapy only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

3.6.2 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 STUDY DRUG

Study drug includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) and can consist of the following:

Table 4-1: Study Drugs for CA209451

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
Nivolumab Solution for Injection	100 mg (10 mg/mL)	IP	Open Label[a]	10 mL/vial (5 or 10 vials/carton)	Store at 2° - 8°C. Protect from light and freezing.
Ipilimumab Solution for Injection	200 mg (5 mg/mL)	IP	Open Label[a]	40 mL/vial (4 vials/carton)	Store at 2° - 8°C. Protect from light and freezing.
0.9% Sodium Chloride for Injection	N/A	IP	Open Label[a]	Various (local commercial product)	As per as per package insert
5% Dextrose for Injection	N/A	IP	Open Label[a]	Various (local commercial product)	As per as per package insert

[a] The term "open label" refers to the medication as it is upon receipt at the pharmacy. The trial will be conducted in a double-blinded fashion.

Pre-medications or medications used to treat infusion-related reactions should be sourced by the investigative sites if available and permitted by local regulations. Solutions used as diluent or placebo (ie, 0.9% Sodium Chloride Injection or 5% Dextrose Injection) should also be sourced by investigative sites if available and permitted by local regulations.

4.1 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, the investigational medicinal products are:

- Nivolumab
- Ipilimumab
- Placebo for nivolumab (0.9% sodium chloride injection or 5% dextrose injection)
- Placebo for ipilimumab (0.9% sodium chloride injection or 5% dextrose injection)

4.2 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. Non-investigational products should be sourced by the investigator sites if available and permitted by local regulations.

4.3 Storage of Study Drug

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.

Study drug not supplied by BMS will be stored in accordance with the package insert.

Please refer to Section 9.2.2 for guidance on IP records and documentation.

Infusion-related supplies (eg, IV bags, in-line filters, 0.9% sodium chloride injection, 5% dextrose injection) will not be supplied by the sponsor and should be purchased locally if permitted by local regulations.

Please refer to the current version of the Investigator Brochure (IB) for complete storage, handling, dispensing, and infusion information for nivolumab, ipilimumab, and matching placebo.

The unblinded pharmacist will obtain treatment assignment by IVRS and prepare blinded drug.

The infusion duration of nivolumab/matching placebo is 30 minutes and for ipilimumab/matching placebo is 90 minutes.

4.4 Method of Assigning Subject Identification

The subject number will be assigned through an interactive voice response system (IVRS) once the subject has signed the informed consent form and is registered. Every subject that signs the informed consent form must be assigned a subject number in IVRS. Specific instructions for using IVRS will be provided to the investigational site in a separate document.

The investigator or designee will register the subject for enrollment by following the enrollment procedures established by BMS. The following information is required for enrollment:

- Date that informed consent was obtained
- Date of birth
- Gender at birth

Once enrolled in IVRS, subjects that have met all eligibility criteria for whom tumor tissue has been shipped to the central lab will be ready for treatment assignment and drug vial (nivolumab versus placebo) assignment through the IVRS. The following information is required for drug vial assignment:

- Subject number
- Date of birth
- Tumor tissue must be available and submitted to the central lab
- ECOG Performance Status: 0 vs 1
- Gender: Male vs Female
- Prophylactic Cranial Irradiation (PCI) following chemotherapy: Yes vs No

Subjects meeting all eligibility criteria will be randomized in a 1:1:1 ratio Arm A (nivolumab), Arm B (nivolumab/ ipilimumab), or Arm C (placebo). Randomization will be achieved using the permuted blocks within each stratum. The randomization schedule will allocate subjects among the 3 treatment arms in a 1:1:1 ratio.

The exact procedures for using the IVRS will be detailed in the IVRS manual.

4.5 Selection and Timing of Dose for Each Subject

The dosing schedule is detailed in Table 4.5-1 and Table 4.5-2.

Table 4.5-1: Blinded Dosing Schedule (Cycles 1 and 2)

1 Cycle = 42 Days = 6 weeks						
	C1D1	**C1D8**	**C1D15**	**C1D22**	**C1D29**	**C1D36**
Arm A (Nivo)	Nivo: 240 mg (24 mL diluted to 100 mL) Ipi pbo: 100 mL	N/A	Nivo: 240 mg (24 mL diluted to 100 mL)	Nivo pbo: 100 mL Ipi pbo: 100 mL	Nivo: 240 mg (24 mL diluted to 100 mL)	N/A
Arm B (Nivo + Ipi)	Nivo: 1 mg/kg (diluted to 100 mL) Ipi: 3 mg/kg (diluted to 100 mL)	N/A	Nivo pbo: 100 mL	Nivo: 1 mg/kg (diluted to 100 mL) Ipi: 3 mg/kg (diluted to 100 mL)	Nivo pbo: 100 mL	N/A
Arm C (Placebo)	Nivo pbo: 100 mL Ipi pbo: 100 mL	N/A	Nivo pbo: 100 mL	Nivo pbo: 100 mL Ipi pbo: 100 mL	Nivo pbo: 100 mL	N/A

Please note instructions below for reduced total volumes for subjects weighing < 35 kg.

Table 4.5-2: Blinded Dosing Schedule (Cycle 3+)

1 Cycle = 14 Days = 2 weeks		
	C3D1	**C3D8**
Arm A (Nivo)	Nivo: 240 mg (24 mL diluted to 100 mL)	N/A
Arm B (Nivo + Ipi)	Nivo: 240 mg (24 mL diluted to 100 mL)	N/A
Arm C (Placebo)	Nivo pbo: 100 mL	N/A

All subjects will be monitored continuously for AEs while on study treatment. Treatment modifications (eg, dose delay, or discontinuation) will be based on specific laboratory and AE criteria, as described in Sections 4.5.3 and 4.5.4.

When study drugs (ipilimumab or nivolumab) or matched placebos are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab or nivolumab placebo is to be administered first. The second infusion will always be the ipilimumab or ipilimumab-placebo study drug, and will start no sooner than 30 minutes after completion of the nivolumab or nivolumab-placebo infusion.

Ipilimumab or ipilimumab-placebo must be diluted to 100 mL 0.9% Sodium Chloride Solution or 5% Dextrose solution. Nivolumab or nivolumab-placebo must be diluted to 100 mL 0.9% Sodium

Chloride Solution or 5% Dextrose solution. The dilution volumes required to maintain the blind are described in Table 4.5-1 and Table 4.5-2.

For weight-based dosing, if the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated. All doses should be rounded up or to the nearest milligram per institutional standard. There will be no dose modifications allowed.

Subjects weighing < 35 kg: For subjects weighing < 35 kg, nivolumab and ipilimumab must be diluted to 50 mL in 0.9% sodium chloride or 5% dextrose solution. Matching placebo volumes must also be 50 mL to maintain the blind.

4.5.1 Dosing Windows

During Cycles 1 and 2:

- Subjects may be dosed no less than 12 days between
  - C1D1 and C1D15
  - C1D15 and C1D29
  - C1D29 and C2D1
  - C2D1 and C2D15
  - C2D15 and C2D29
  - C2D29 and C3D1
- Subjects may be dosed no less than 5 days between
  - C1D15 and C1D22
  - C1D22 and C1D29
  - C2D15 and C2D22
  - C2D22 and C2D29

During Cycle 3 and beyond:

- Subjects may be dosed no less than 12 days from the previous dose of drug

Subjects may be dosed up to 3 business days after the scheduled date if necessary, or longer in the event of a toxicity requiring dose delay. Subsequent dosing should be based on the actual date of administration of the previous dose of drug.

Treatment compliance will be monitored by drug accountability as well as the subject's medical record and eCRF.

4.5.2 Study Medications

4.5.2.1 Nivolumab Monotherapy (Arm A)

For subjects randomized to Arm A, nivolumab 240 mg will be administered every 2 weeks as a 30 min IV infusion until progression, unacceptable toxicity, withdrawal of consent, completion of 24 months of treatment, or the study ends, whichever occurs first. Subjects should begin study treatment within 3 business days of randomization. The rationale for this dosage schedule is

provided in Section 1.1.6. In order to maintain a blinded study, the schedule of investigational and placebo treatments is divided into two 42-day cycles at the start of therapy, followed by ongoing 2-week cycles. This dosing schedule is described in detail in Table 4.5-1 and Table 4.5-2.

Refer to the Investigator Brochure for more detail. There are no pre-medications recommended on the first cycle. If an acute infusion reaction is noted, subjects should be managed according to Section 4.5.6.

See Section 4.5.4 for information on Management Algorithms for Immuno-Oncology Agents.

4.5.2.2 Nivolumab and Ipilimumab Combination Therapy (Arm B)

For subjects randomized to Arm B, nivolumab/placebo 1 mg/kg (30 min IV infusion) and ipilimumab 3 mg/kg (90 minute IV infusion) will be administered every 3 weeks for 4 doses, followed by nivolumab 240 mg every 2 weeks until progression, unacceptable toxicity, withdrawal of consent, completion of 24 months of treatment, or the study ends, whichever occurs first. Subjects should begin study treatment within 3 business days of randomization. The rationale for this dosage schedule is provided in Section 1.1.7. In order to maintain a blinded study, the schedule of investigational and placebo treatments is divided into two 42-day cycles at the start of therapy, followed by ongoing 2-week cycles. This dosing schedule is described in detail in Table 4.5-1 and Table 4.5-2.

Refer to the Investigator Brochure for more detail. There are no pre-medications recommended on the first cycle. If an acute infusion reaction is noted, subjects should be managed according to Section 4.5.6.

See Section 4.5.4 for information on Management Algorithms for Immuno-Oncology Agents.

4.5.2.3 Placebo Therapy (Arm C)

For subjects randomized to Arm C, placebo (0.9% Sodium Chloride Solution or 5% Dextrose) will be administered as described in Table 4.5-1 and Table 4.5-2.

4.5.3 Dose Modifications and Delays

4.5.3.1 Dose Modifications

Dose reductions for the management of toxicities of individual subjects or dose escalations are not permitted. All dose modification rules apply to all treatment arms given the blinded nature of this study.

4.5.3.2 Dose Delays

Dose delay criteria apply for all drug-related adverse events (regardless of whether or not the event is attributed to nivolumab, ipilimumab, or both). All blinded study drugs must be delayed until treatment can resume.

Dose delay criteria also apply for the placebo version of each agent, given the blinded nature of this study.

Blinded study therapy administration should be delayed for the following:

- Grade 2 non-skin, drug-related adverse event, with the exception of fatigue
- Grade 2 drug related creatinine, AST, ALT and/or Total Bilirubin abnormalities
- Any Grade 3 skin, drug-related adverse event
- Any Grade 3, drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia does not require dose delay
  - Grade ≥ 3 drug related amylase or lipase abnormality that are not associated with symptoms or clinical manifestations of pancreatitis do not require a dose delay
  - Grade ≥ 3 drug related AST, ALT, or total bilirubin will require dose discontinuation (see section 4.5.3.3 and section 4.5.3.4)
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of blinded study medication

Subjects who require delay of nivolumab should be re-evaluated weekly or more frequently as clinically indicated and resume nivolumab dosing when re-treatment criteria are met.

4.5.3.3 Criteria to Resume Treatment

Subjects may resume treatment with blinded study therapy when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- Subjects with Grade 2 AST/ALT and/or total bilirubin abnormalities may resume treatment when laboratory values return to baseline and management with corticosteroids, if needed is complete.
- Subjects with a combined Grade 2 AST/ALT AND Total Bilirubin values meeting discontinuation criteria (section 4.5.3.4) should have treatment permanently discontinued
- Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the BMS Medical Monitor
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled timepoint per protocol. Doses should not be skipped. In particular, this is to ensure that subjects in Arm B will receive 4 administrations of combined nivolumab and ipilimumab treatment if toxicity allows.

If treatment is delayed > 6 weeks (42 days) from the last dose due to blinded study drug-related toxicity, the subject must be permanently discontinued from blinded study therapy, except as specified in Section 4.5.3.4. In the event treatment is delayed > 6 weeks due to reasons other than blinded study drug-related toxicity, the case should be discussed with the Medical Monitor before proceeding.

4.5.3.4 Discontinuation Criteria

Treatment with blinded study therapy should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related AE lasting > 7 days, with the following exceptions:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, myocarditis, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Grade ≥ 3 drug-related AST.ALT or Total Bilirubin requires discontinuation
    - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN

*In most cases of Grade 3 AST or ALT elevation, study drug(s) will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ration that warrants continuation of study drug(s), a discussion between the investigator and the BMS Medical Monitor/designee must occur.

- Any Grade 4 drug-related AE or laboratory abnormality, except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations, or radiographic signs of pancreatitis.
  - For Grade 4 endocrinopathy AEs such as hyper or hypothyroidosis, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (steroids, thyroid hormones) or glucose controlling agents, respectively, retreatment can be considered after discussion with the BMS Medical Monitor.

- Any dosing delays lasting > 6 weeks from the last dose with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed. Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks from the last dose, the BMS Medical Monitor must be consulted
  - Dosing delays > 6 weeks from the last dose that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued blinded study therapy dosing

Tumor assessments for all subjects should continue as per protocol even if blinded study therapy dosing is delayed. Periodic study visits to assess safety and laboratory studies should continue at least every 6 weeks or more frequently if clinically indicated during such dosing delays.

4.5.4 Management Algorithms for Immuno-Oncology Agents

Immuno-oncology agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab and ipilimumab are considered an immuno-oncology agents in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Management algorithms have been developed to assist investigators in assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathies
- Skin
- Neurological

While the ipilimumab investigator brochure contains very similar safety management algorithms for these adverse events, the recommendation is to follow the nivolumab algorithms for immune-oncology agents (I-O) in order to standardize the safety management across the three blinded treatment arms.

The algorithms are found in the Nivolumab Investigator Brochure and Appendix 2 of this protocol.

4.5.5 Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease (PD).[35] The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued blinded study therapy.

Subjects will be permitted to continue treatment beyond initial RECIST 1.1 defined PD as long as all of the following criteria are met and clearly documented:

- Investigator-assessed clinical benefit and no rapid disease progression;
- Tolerating blinded study drug(s);
- Stable performance status;
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression
- Subject provides written informed consent prior to receiving additional blinded study therapy, using an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options

All decisions to continue treatment beyond initial progression must be discussed with the Medical Monitor and documented in the study records. The subject will continue to receive monitoring according to the Time and Events Schedules in Table 5.1-2 and Table 5.1-3.

A radiographic assessment should be performed within 6 weeks of original PD to determine whether there has been a decrease in the tumor size, or continued PD.

For the subjects who continue blinded study therapy beyond PD, further progression is defined as an additional 10% increase in tumor burden from time of initial PD. This includes an increase in the sum of all target lesions and/ or the development of new measurable lesions. For subjects with evaluable disease only, further progression is defined as unequivocal disease progression of non-target lesions or the development of new lesions from time of initial PD. Treatment should be discontinued permanently upon documentation of further disease progression.

New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden measurement if the longest diameter increases to at least 10 mm (except for pathological lymph nodes, which must have an increase in short axis to at least 15 mm).

For statistical analyses that include the investigator-assessed progression date, subjects who continue treatment beyond initial investigator-assessed, RECIST 1.1-defined progression will be considered to have investigator-assessed progressive disease at the time of the initial progression event.

For subjects in all treatment arms, global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression (ie, radiographic confirmation) even after discontinuation of treatment.

4.5.6 Treatment of Nivolumab- or Ipilimumab-Related Infusion Reactions

Since nivolumab and ipilimumab contain only human immunoglobulin protein sequences, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a

reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as a serious adverse event (SAE) if criteria are met. Infusion reactions should be graded according to NCI CTCAE (version 4.0) guidelines.

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

For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated)

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

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

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

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

- Immediately discontinue infusion of blinded study therapy. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with

methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Blinded study therapy will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms.

In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids)

4.6 Blinding/Unblinding

The Sponsor, subjects, investigator and site staff will be blinded to the study therapy administered. Each investigative site must assign an unblinded pharmacist/designee, and an unblinded site monitor will be assigned to provide oversight of drug supply and other unblinded study documentation.

Designated staff and associates of the Sponsor may be unblinded prior to database lock to facilitate the bioanalytical analysis of pharmacokinetic samples and immunogenicity. A bioanalytical scientist in the Bioanalytical Sciences department of Bristol-Myers Squibb Research & Development (or a designee in the external central bioanalytical laboratory) may be unblinded to the randomized treatment assignments in order to minimize unnecessary bioanalytical analysis of samples.

Blinding of treatment assignment is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual subject in which knowledge of the investigational product is critical to the subject's management, the blind for that subject may be broken by the investigator. The subject's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

Before breaking the blind of an individual subject's treatment, the investigator should determine that the unblinded information is necessary, ie, that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not related to the investigational product, the problem may be properly managed by assuming that the subject is receiving active product. It is highly desirable that the decision to unblind treatment assignment be discussed with the Medical Monitor, but the investigator always has ultimate authority for the decision to unblind. The Principal Investigator should only call in for emergency unblinding AFTER the decision to discontinue the subject has been made.

Emergency unblinding is available as an option in the IVRS. Consult IVRS Manual for instructions on Emergency unblinding).

In cases of accidental unblinding, contact the Medical Monitor and ensure every attempt is made to preserve the blind. Any request to unblind a subject for non-emergency purposes should be discussed with the Medical Monitor.

4.7 Treatment Compliance

Treatment compliance will be monitored by drug accountability as well as the subject's medical record and CRF.

4.8 Destruction or Return of Investigational Product

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

If	Then
IP supplied by BMS (including its vendors)	Any unused IP supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless IP containers must be immediately destroyed as required for safety, or to meet local regulations (e.g., cytotoxics or biologics). If IP will be returned, the return will be arranged by the responsible Study Monitor.
IP sourced by site, not supplied by BMS (or its vendors) (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal, 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. The following minimal standards must be 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

It is the investigator's or designee's responsibility to arrange for disposal of all empty containers.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of IP provided by BMS (or its vendors). Destruction of non-IP sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

Please refer to Section 9.2.2 for guidance on IP records and documentation.

4.9 Retained Samples for Bioavailability / Bioequivalence

Not Applicable

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Procedural Outline (CA209451)

Procedure	Screening	Notes
Eligibility Assessments		
Informed Consent	X	Informed Consent may be obtained at any time, provided it is prior to conduct of any study-related procedures. Note that SAEs are collected from the date of consent.
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening and confirmed prior to randomization
Medical History	X	
Prior Systemic Therapy	X	
Safety Assessments		
Physical Examination	X	
Physical Measurements	X	Include Height, Weight, and ECOG performance Status. Within 14 days prior to randomization
Vital Signs and Oxygen saturation	X	Temperature, BP, HR, and O2 saturation at rest by pulse oximetry. Obtain vital signs at the screening visit and within 72 hours prior to randomization.
Assessment of Signs and Symptoms	X	Within 14 days prior to randomization
Concomitant Medication Collection	X	Within 14 days prior to randomization
Laboratory Tests	X	CBC with differential, Chemistry panel including LDH, AST, ALT, ALP, T.Bili, BUN or serum urea level, uric acid, creatinine, Ca, Mg, Na, K, Cl, P, glucose, bicarbonates (optional), albumin, amylase or lipase, TSH (reflex to free T3, free T4 for abnormal TSH result), hepatitis B surface antigen (HBV sAg), and hepatitis C antibody (HCV Ab) within 14 days prior to randomization. Screening labs done within 72 hours prior to first dose can also be used for on treatment lab purposes at Day 1 dosing.
ECG	X	Within 28 days prior to randomization
Pregnancy Test	X	Performed within 24 hours prior to first dose for WOCBP only (serum or urine - local/site)

Table 5.1-1: Screening Procedural Outline (CA209451)

Procedure	Screening	Notes
Efficacy/Biomarker Assessments		
Radiographic Tumor Assessment	X	CT/ Chest, CT/MRI Abdomen, Pelvis, and any other known sites of disease; MRI/CT Brain (refer to section 5.4 for detail on cases where CT of the Brain is acceptable) Within 21 days prior to randomization. Additional sites of known or suspected disease (including CNS) should be imaged at the screening visit and at subsequent on-study assessments.
Collection of tumor tissue for biomarker evaluation	X	See Section 3.3.1, Inclusion 2f
IVRS/Clinical Drug Supplies		
Phone calls to IVRS		Phone calls must be made to IVRS as follows: Screening phone call to IVRS: For subject number assignment at the time informed consent is obtained.

Table 5.1-2: On-Treatment Assessments for All Subjects, Cycle 1-2 [Cycle length 42 days]

Procedure	Cycle 1-2 Day 1	Cycle 1 Day 8	Cycle 1-2 Day 15	Cycle 1-2 Day 22	Cycle 1-2 Day 29	Notes
Safety Assessments						
Targeted Physical Examination	X		X	X	X	Within 72 hours prior to dosing
Vital Signs and Oxygen Saturation	X		X	X	X	Temperature, BP, HR, O2 saturation at rest by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable) within 72 hours prior to dosing and at any time a subject has any new or worsening respiratory symptoms
Physical Measurements	X		X	X	X	Includes Weight and ECOG performance status within 72 hours prior to dosing
Adverse Events Assessment	---------- Continuously ----------					Assessed using NCI CTCAE v. 4.0. SAEs should be approved in TAO within 5 days from entry
Review of Concomitant Medications	X		X	X	X	
Extended Laboratory Tests	X		X		X	Extended on-study local laboratory assessments should be done within 72 hours prior to dosing on Days 1, 15, 29 and include: CBC with differential, uric acid, BUN or serum urea level, creatinine, Na, K, Ca, Mg, phosphorus, chloride, bicarbonate (optional), amylase or lipase, glucose, AST, ALT, total bilirubin, alkaline phosphatase, LDH.
Limited Laboratory Tests				X		Limited on-study local laboratory assessment should be done within 72 hours prior to dosing on Days 22 and include: CBC with differential, AST, ALT, total bilirubin, alkaline phosphatase and creatinine.
Thyroid Function Testing	X					TSH (reflex to free T3 and free T4 if abnormal result) to be performed). (Day 1 of Cycle 1 & 2 or within 72 hours prior to dosing)
Pregnancy Test	X	See Note				Serum or urine within 24 hours prior to first dose and then at least once every 4 weeks regardless of dosing schedule.

Table 5.1-2: On-Treatment Assessments for All Subjects, Cycle 1-2 [Cycle length 42 days]

Procedure	Cycle 1-2 Day 1	Cycle 1 Day 8	Cycle 1-2 Day 15	Cycle 1-2 Day 22	Cycle 1-2 Day 29	Notes
Efficacy Assessments						
Radiographic Tumor Assessment	See Note					CT chest, CT/MRI abdomen, and any other known or suspected sites of disease. Repeat CT/MRI of pelvis is required for subjects with pelvic metastases at baseline, or if clinically indicated Subjects with a history of brain metastasis should have surveillance MRI/CT of the brain (refer to section 5.4 for detail on cases where CT of the Brain is acceptable) every 6 weeks, or sooner if clinically indicated. See Table 5.4-1 for CT and MRI scan schedule.
Additional Exploratory Biomarker Testing						
Serum Whole Blood Tumor Biopsy	See Note					See Table 5.6-1 of Biomarker Sampling Schedule
PK and Immunogenicity Assessments						
PK samples	See Note					See Table 5.5-1 of PK and Immunogenicity Sampling
Immunogenicity samples	See Note					See Table 5.5-1 of PK and Immunogenicity Sampling
Outcomes Research Assessments						
Patient Reported Outcomes (PRO)	X		X	X	X	For on-treatment visits: Assessments (Lung Cancer Symptom Scale and EQ-5D) will be performed on treatment day prior to study treatment.
Health Resource Utilization	X		X	X	X	Except cycle 1. Note that concomitant medication collection will be included.

Table 5.1-2: On-Treatment Assessments for All Subjects, Cycle 1-2 [Cycle length 42 days]

Procedure	Cycle 1-2 Day 1	Cycle 1 Day 8	Cycle 1-2 Day 15	Cycle 1-2 Day 22	Cycle 1-2 Day 29	Notes
Clinical Drug Supplies						
Randomization	X					Call IVRS for randomization
Administer Blinded Study Drug	X		X	X	X	IVRS should be called within 1 day prior to blinded study therapy administration to receive vial assignment. Note: The subject must receive the blinded study medication within 3 business days after vial assignment. See section 4.5.1 for minimum dosing intervals between Cycles. A call to IVRS is made for every dosing visit.

Table 5.1-3: On-Treatment Assessments for All Subjects, Cycle 3 and subsequent cycles [Cycle 3+ length 14 days] (CA209451)

Procedure	Cycle 3 and subsequent cycles, Day 1	Notes
Safety Assessments		
Targeted Physical Examination	X	Within 72 hours prior to dosing
Vital Signs and Oxygen Saturation	X	Temperature, BP, HR, O2 saturation at rest by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable) within 72 hours prior to dosing and at any time a subject has any new or worsening respiratory symptoms
Physical Measurements	X	Includes Weight and ECOG performance status within 72 hours prior to dosing
Adverse Events Assessment	Continuously	Assessed using NCI CTCAE v. 4.0. SAEs should be approved in TAO within 5 days from entry
Review of Concomitant Medications	X	
Extended Laboratory Tests	X (See note: Alternate Cycles 3, 5, 7, 9, etc)	Extended on-study local laboratory assessments should be done within 72 hours prior to dosing for Cycle 3 and every alternate dose thereafter (Cycles 5, 7, 9, 11 etc.) and include: CBC with differential, uric acid, BUN or serum urea level, creatinine, Na, K, Ca, Mg, phosphorus, chloride, bicarbonate (optional), amylase or lipase, glucose, AST, ALT, total bilirubin, alkaline phosphatase, LDH.
Limited Laboratory Tests	X (see note: Alternate Cycles 4, 6, 8, 10, 12, etc)	Limited on-study local laboratory assessment should be done within 72 hours prior to dosing (beginning at Cycle 4 and every alternate dose thereafter (Cycles 6, 8, 10, 12, etc.) and include: CBC with differential, AST, ALT, total bilirubin, alkaline phosphatase and creatinine.
Thyroid Function Testing	X See Note (every 3 Cycles)	TSH (reflex to free T3 and free T4 if abnormal result) to be performed every 3rd cycle within 72 hours prior to dosing. (C3D1, C6D1, C9D1, etc)
Pregnancy Test	X See Note	Serum or urine at least once every 4 weeks regardless of dosing schedule.

Table 5.1-3: On-Treatment Assessments for All Subjects, Cycle 3 and subsequent cycles [Cycle 3+ length 14 days] (CA209451)

Procedure	Cycle 3 and subsequent cycles, Day 1	Notes
Efficacy Assessments		
Radiographic Tumor Assessment	See Note	CT chest, MRI/CT brain, abdomen, and any other known or suspected sites of disease,. Repeat CT/MRI of pelvis is required for subjects with pelvic metastases at baseline, or if clinically indicated (refer to section 5.4 for detail on cases where CT of the Brain is acceptable). Tumor assessments will be conducted every 6 weeks (± 5 days) for the first 36 weeks then every 12 weeks (± 5 days) or sooner if clinically indicated until disease progression. See Table 5.4-1 for CT and MRI scan schedule
Additional Exploratory Biomarker Testing		
Serum Whole Blood Tumor Biopsy	See Note	See Table 5.6-1 of Biomarker Sampling Schedule
PK and Immunogenicity Assessments		
PK samples	See Note	See Table 5.5-1 of PK and Immunogenicity Sampling
Immunogenicity samples	See Note	See Table 5.5-1 of PK and Immunogenicity Sampling
Outcomes Research Assessments		
Patient Reported Outcomes (PRO)	X	For on-treatment visits: Assessments (Lung Cancer Symptom Scale and EQ-5D) will be performed on treatment day prior to study treatment. Assessments will be performed at each cycle on Day 1 for the remainder of the first 6 months on study, then every 6 weeks thereafter for the remainder of the treatment period.
Health Resource Utilization	X	Except cycle 1. Note that concomitant medication collection will be included.
Clinical Drug Supplies		
Administer Blinded Study Drug	X	IVRS should be called within 1 day prior to blinded study drug administration to receive vial assignment. Note: The subject must receive the blinded study therapy within 3 business days of vial assignment. See Section 4.5.1 for minimum dosing intervals between Cycles. A call to IVRS is made for every dosing visit.

Table 5.1-4: Follow-Up Assessments for All Subjects (CA209451)

Procedure	Follow-Up[a] Visits 1 and 2	Survival Follow-Up[b] Visits	Notes
Safety Assessments			
Targeted Physical Examination	X		To assess for potential late emergent study drug related issues
Adverse Events Assessment	X	X	NSAEs and SAEs must be collected up to 100 days after blinded study drug discontinuation. SAEs that relate to any later protocol specified procedure must be collected. SAEs should be approved in TAO within 5 days from entry.
Review of Concomitant Medication	X	X	Collection of concomitant medications only for treatment-related AEs or SAEs until the medication is discontinued.
Extended Laboratory Tests	X		CBC with differential, uric acid, BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, chloride, phosphorus, bicarbonate (optional), amylase or lipase, glucose, AST, ALT, total bilirubin, alkaline phosphatase, LDH
Thyroid Function Testing	X		TSH (reflex to free T3 and free T4 if abnormal result)
Pregnancy Test	X		Serum or urine
Efficacy Assessments			
Radiographic Tumor Assessment CT/MRI	See Note	See note	See Table 5.4-1 for CT/MRI
Outcomes Research Assessments			
Patient Reported Outcomes (PRO)	X	EQ-5D only	Both the Lung Cancer Symptom Scale and EQ-5D will be given in FU Visits 1 & 2. In Survival Visits, EQ-5D is collected every 3 months for the first year of the Follow-up Phase, then every 6 months thereafter. For Survival Visits these can be collected in person or via telephone contact.
Healthcare resource utilization	X		

Table 5.1-4: Follow-Up Assessments for All Subjects (CA209451)

Procedure	Follow-Up[a] Visits 1 and 2	Survival Follow-Up[b] Visits	Notes
Exploratory Biomarker Testing			
Serum	See Note.		Collection of Biomarker samples at time of progression is optional. See Table 5.6-1 of Biomarker Sampling Schedule.
Whole Blood			
Tumor Biopsy			
Subject Status			
Survival Status	X	X	Every 3 months after X02; may be accomplished by visit or phone contact, to update survival information and assess subsequent anti-cancer therapy.

[a] Follow-up visits occur as follows: X01 = 35 days ± 7 days from last dose, X02 = 80 days ± 7 days from X01

[b] Survival visits continue every 3 months ± 14 days after Follow-up Visit 2 until death, lost to follow-up, or withdrawal of study consent

5.1.1 Retesting During Screening

Retesting of laboratory parameters and/or other assessments within the Screening period will be permitted (in addition to any parameters that require a confirmatory value).

Any new result will override the previous result (ie, the most current result prior to Randomization) and is the value by which study inclusion will be assessed, as it represents the subject's most current, clinical state.

Laboratory parameters and/or assessments that are included in Table 5.1-1, Screening Procedural Outline may be repeated in an effort to find all possible well-qualified subjects. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

5.2 Study Materials

The following materials will be provided to the site by BMS.

- NCI CTCAE version 4.0
- Nivolumab Investigator Brochure
- Ipilimumab Investigator Brochure
- Pharmacy Binder
- Laboratory manuals for collection and handling of blood (including biomarker and immunogenicity) and tissue specimens
- Site manual for operation of interactive voice response system, including enrollment worksheets
- Imaging Manual for image acquisition and submission to central vendor
- Manual for entry of local laboratory data
- Pregnancy Surveillance Forms
- Serious Adverse Events (or eSAE) case report forms
- Lung Cancer Symptom Score and EuroPRO Group's EQ-5D questionnaires

5.3 Safety Assessments

Safety assessments include AEs, physical examinations, vital signs, ECOG performance status, assessment of signs and symptoms, laboratory tests, pregnancy tests as outlined in Section 5.1.

Some of the previously referred to assessments may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

5.3.1 *Imaging Assessment for the Study*

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the Study Investigator as per standard medical/clinical judgment.

5.4 Efficacy Assessments

Study evaluations will take place in accordance with the flow charts in Section 5.1.

Contrast-enhanced computed tomography (CT) of the chest and CT or magnetic resonance imaging (MRI) of abdomen, and any other known or suspected sites of disease are the preferred methods of radiographic assessment of tumors. Repeat CT/MRI of pelvis is required for subjects with pelvic metastases at baseline, or if clinically indicated. Brain MRI scan is the preferred imaging method for evaluating CNS metastasis, and assessment is required at screening, however CT of the brain is acceptable if MRI is contraindicated. If a subject has a known allergy to contrast material, please use local prophylaxis standards to obtain the assessment with contrast if at all possible, or use the alternate modality. In cases where contrast is strictly contraindicated, a non-contrast scan will suffice.

All known or suspected sites of disease (including CNS) should be assessed at screening and at subsequent assessments using the same imaging method and technique. If more than one method is used at screening, then the most accurate method according to RECIST 1.1 should be used when recording data, and should again be used for all subsequent assessments.

Bone scan, PET scan, or ultrasound are not adequate for assessment of RECIST 1.1 response. In selected circumstances where such modalities are the sole modality used to assess certain non target organs, those non target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

Previously treated CNS metastases are not considered measurable lesions for purposes of RECIST 1.1 response. Subjects with a history of brain metastasis should have surveillance MRI/CT approximately every 6 weeks up to 36 weeks and then every 12 weeks, or sooner if clinically indicated.

Baseline assessments should be performed within 21 days of randomization.

Subjects will be evaluated for tumor response beginning 6 weeks from the date of randomization (± 5 days), then every 6 weeks (± 5 days) thereafter up to 36 weeks. Beyond Week 36, tumor assessments will be performed every 12 weeks (± 5 days), or more frequently as clinically indicated or per local Standard of Care, until disease progression (or until discontinuation of study drug in subjects receiving blinded study therapy beyond progression), lost to follow-up, withdrawal of study consent, or the study ends. See Table 5.4-1 for a schedule of tumor assessments. Tumor assessments for all subjects should continue as per protocol even if dosing is delayed. Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible.

Tumor imaging assessments for ongoing study treatment decisions will be completed by the investigator using RECIST 1.1 criteria; see Appendix 3.

Table 5.4-1: Schedule of CT/MRI Tumor Assessments

Time On Study	Assessment Frequency	Assessment Week (Day 1 of Week Shown)	Assessment Window
Baseline		Week 0	– 21 days
Between Week 6 and Week 36	Every 6 weeks	6, 12, 18, 24, 30, 36	± 5 days
Beyond Week 36	Every 12 weeks	48, 60, 72+	± 5 days

5.4.1 Use of CT Component of a PET/CT Scan

Combined modality scanning such as with FDG-PET/CT is increasingly used in clinical care, and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change rather quickly with time. At present, low dose or attenuation correction CT portions of a combined FDG-PET/CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically based RECIST diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the FDG-PET/CT can be used for RECIST v1.1 measurements. Note, however, that the FDG-PET/CT portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

5.4.2 Primary and Secondary Efficacy Assessments

The primary endpoint is to compare OS in subjects randomized to nivolumab in combination with ipilimumab, versus subjects randomized to placebo. The secondary endpoints are to compare OS of nivolumab versus placebo, to compare BICR-assessed PFS of nivolumab and nivolumab combined with ipilimumab versus placebo, and to evaluate (descriptively) OS and BICR-assessed PFS of nivolumab combined with ipilimumab versus nivolumab monotherapy. See Section 8.3 for the definition of OS and PFS.

Every effort will be made to collect survival and imaging data on all subjects, including subjects withdrawn from treatment for any reason, who are eligible to participate in the study and who have not withdrawn consent for additional data collection. If the death of a subject is not reported, all dates in this study representing a date of subject contact will be used in determination of the subject's last known date alive.

5.5 Pharmacokinetic Assessments

Table 5.5-1: Pharmacokinetic (PK) and Immunogenicity Sample Collections

Part[a]	Study Day 1 Cycle = 6 Weeks (Part A) 1Cycle=2 Weeks (Part B)	Time (Relative to Dosing) Hour	Time (Relative to Dosing) Hour: Min	Pharmacokinetic Blood Samples for Nivolumab	Immunogenicity Blood Samples for Nivolumab	Pharmacokinetic Blood Samples for Ipilimumab	Immunogenicity Blood Samples for Ipilimumab
A	C1D1	0 (predose)[b]	00:00	X	X	X	X
A	C1D22	0 (predose)[b]	00:00	X	X	X	X
A	C2D22	0 (predose)[b]	00:00	X	X	X	X
B	C9D1	0 (predose)[b]	00:00	X	X	X	X
B	C17D1	0 (predose)[b]	00:00	X	X	X	X
B	C25D1	0 (predose)[b]	00:00	X	X	X	X
B	D1 of every 12th cycle after C25D1until end of study treatment or up to 2 years of treatment	0 (predose)[b]	00:00	X	X	X	X

a Part A indicates first 12 weeks of treatment (nivolumab + ipilimumab dosing). Part B indicates nivolumab monotherapy period starting from Week 13.

b Predose (0 Hour) samples may be collected up to 4 days prior to dosing. However, if a predose sample is collected, and the dose is subsequently delayed, an additional predose sample should not be collected.

Samples for PK and immunogenicity assessments will be collected from study subjects assigned to all 3 treatment arms at the time points indicated in Table 5.5-1. All on-treatment PK timepoints are intended to align with days on which nivolumab/ nivolumab placebo is administered. If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected, but the dose is subsequently delayed, an additional predose sample should not be collected. Separate, detailed instructions for the collection, processing, handling, labeling, storage, and shipment of PK and immunogenicity samples will be provided in the central lab manual.

5.6 [redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]	
[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.6.1 [redacted]

[redacted]

5.6.1.1 Tumor Mutational Burden

To explore the potential association of tumor mutational burden with clinical outcomes, tumor tissue will be evaluated by using FoundationOne CDx™ (F1CDx) assay, a comprehensive genomic profile (CGP) assay based on baseline tumor tissue.

[redacted]

[redacted]

[redacted]

5.7 Outcomes Research Assessments

The evaluation of health related quality of life is an increasingly important aspect of a clinical efficacy. Such data provides an understanding of the impact of treatment from the subjects' perspective and offers insights into the patient experience that may not be captured through physician reporting. Generic health related quality of life scales additionally provide data necessary in calculating utility values for health economic models. The EQ-5D will be collected in order to assess the impact of study treatment on generic health related quality of life, which will also be used in populating health economic models most notably, cost effectiveness analysis.

The Lung Cancer Symptom Scale (LCSS) will be collected to assess the impact of study treatment on patient reported disease related symptoms (See Appendix 4). The Lung Cancer Symptom Scale is a validated instrument designed to assess the impact of treatment on disease-related symptoms. It consists of 6 symptom specific questions related to dyspnea, cough, fatigue, pain, hemoptysis and anorexia plus 3 summary items: symptom distress, interference with activity, and global health related quality of life (HRQoL). The degree of impairment is recorded on a 100 mm visual analogue scale with scores from 0 to 100 with zero representing the best score.

General health status will be measured using the EQ-5D (EQ-5D-3L See Appendix 5). The EQ-5D is a standardized instrument for use as a measure of self-reported health status. The EQ-5D comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety) and a visual analog rating scale (VAS). The utility data generated from the EQ-5D is recommended for and commonly used in cost effectiveness analysis.

Healthcare resource utilization data (eg, hospitalizations, non-protocol specified medical visits, diagnostics, etc) will be collected for all randomized subjects. The resource utilization capture is specific to hospital admission utilization data and non-protocol specified visits related to study therapy.

5.8 Other Assessments

5.8.1 [redacted]

[redacted]

[redacted]

5.8.2 Blinded Independent Central Review (BICR)

A Blinded Independent Central Review will be performed for randomized subjects to determine RECIST 1.1 response for the analysis of PFS and ORR. Details of the Imaging responsibilities and procedures will be specified in the Imaging charter. Tumor assessments should be submitted to the third-party BICR vendor as they are performed on an ongoing basis.

Sites will be informed of quality issues or the need for repeat scanning via queries from the central imaging vendor. Results of Central Imaging analysis will not be returned to the site.

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 blinded study drug 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 blinded study drug, whether or not considered related to the blinded study drug.

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

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

BMS will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320.

6.1 Serious Adverse Events

A S***erious 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.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

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

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) 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 blinded 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).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

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 blinded 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 100 days of discontinuation of dosing. For subjects who are randomized but never treated with study drug, SAEs should be collected for 30 days from the date of randomization. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

The investigator must report any SAE that occurs after these time periods and that is believed to be related to blinded study drug or protocol-specified procedure.

An SAE report must be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to blinded study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship must be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to blinded study drug, and pregnancies must be reported to BMS (or designee) within 24 hours of awareness of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. In the event the electronic system is unavailable for transmission, paper forms must be used and submitted immediately. When paper forms are used, the original paper forms are to remain on site.

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 must include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to blinded study drug or if new information becomes available, the SAE report must be updated and submitted within 24 hours to Sponsor or designee using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

BMS will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal regulations 21 CFR Parts 312 and 320. A Suspected Unexpected Serious Adverse Reaction (SUSAR) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

6.2 Nonserious Adverse Events

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

6.2.1 Nonserious Adverse Event Collection and Reporting

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

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 blinded study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

All nonserious AEs (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment.

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

6.2.2 Immune-Mediated Adverse Events

Immune-mediated adverse events are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. IMAEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the participant's case report form.

Every adverse event must be assessed by the investigator with regard to whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information will be collected on the participant's case report form.

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) 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 blinded study 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).

6.4 Pregnancy

If, following initiation of the blinded 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 blinded study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy.

In the rare event that the benefit of continuing blinded study drug is thought to outweigh the risk, after consultation with BMS, the pregnant subject may continue blinded 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 must be performed on the subject.

The investigator must immediately notify the BMS (or designee) Medical monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours of awareness of the event 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 Sponsor or designee. In order for BMS to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 Overdose

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

6.6 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1 for reporting details).

Potential drug induced liver injury is defined as:

1. AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)
   AND
2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),
   AND
3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic

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

A Data Monitoring Committee (DMC) will be utilized to provide general oversight and safety considerations for this study. The DMC will provide advice to the Sponsor regarding actions the committee deems necessary for the continuing protection of subjects enrolled in this study. The DMC will be charged with assessing such actions in light of an acceptable risk/benefit profile for nivolumab monotherapy and nivolumab in combination with ipilimumab. The DMC will act in an advisory capacity to BMS and will monitor subject safety data for the study approximately every 6 months for the duration of the trial.

The DMC will be advisory to the clinical study leadership team. The clinical study leadership will have responsibility for overall conduct of the study including managing the communication of study data. The group will be responsible for promptly reviewing the DMC recommendations, for providing guidance regarding the continuation or termination of the study, and for determining whether amendments to the protocol or changes to the study conduct are required.

Details of the DMC responsibilities and procedures will be specified in the DMC charter.

When required, adjudicated events will be submitted to the DMC and Health Authorities for review on a specified timeframe in accordance with the adjudication documentation.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

Per original protocol, approximately 810 subjects were to be randomized to the three treatment arms in a 1:1:1 ratio.

The primary objective is to compare Overall Survival (OS) of nivolumab in combination with ipilimumab versus placebo. The analysis of primary endpoint of OS will be conducted when at least 386 deaths have been observed pooled across the two treatment groups. Using accrual and treatment effect assumptions described below, it is expected that 208 events will be observed in placebo and 178 in nivolumab in combination with ipilimumab treatment groups. With 386 events available for comparison of OS in nivolumab in combination with ipilimumab vs placebo groups, power of the log-rank test is approximately 90% to detect a hazard ratio (HR) of 0.72 with a type I error of 0.05 (two-sided). The critical hazard ratio for determining whether nivolumab in combination with ipilimumab is superior to placebo is 0.82.

Power calculations were performed using EAST® Software (version 6.4.1). Results were generated by 10000 simulations. Model assumptions were as follows:

Survival function for placebo arm was modeled using a four hazard pieces: OS rates at 3, 9, 18 and 26 months were assumed to be 90%, 47%, 15% and 9%, respectively, based on published survival curve for placebo maintenance in Extensive-Stage SCLC, adjusted for induction phase [36]. Median OS for placebo was 8.8 months.

For nivolumab in combination with ipilimumab, a delayed effect versus placebo with a hazard ratio (HR) of 1 for the first 3 months [37]and an HR of 0.68 thereafter was assumed, resulting into overall HR (experim vs placebo) of 0.72 at time of the OS analysis. Median OS for the experimental arm was 11.0 months.

Accrual information used in the simulations had the same pattern as the actual data at time of the protocol amendment (832 subjects were accrued in 28 months and randomized to the three treatment groups). A 5% probability of dropout by month 6 was taken into account. Given the observed accrual and dropout and survival assumptions it is expected that the duration of the study from start of randomization to final analysis will be approximately 35 months (28 months of accrual + 7 months of minimum follow-up , providing an average follow up of 9 months).

This study includes a sub-study to allow enrollment of patients from China (site-specific protocol amendment 12). Data from these additional subjects will be reported separately. Subjects from China randomized on or before end of global study accrual will be included in the population used for the primary analysis clinical study report. The required number of deaths for the primary OS analysis is based on the global study population.

The independent Data Monitoring Committee (DMC) will have access to periodic interim safety and efficacy reports to allow for a risk/benefit assessment.

8.2 Populations for Analyses - Data set descriptions

- Global study population: all subjects enrolled during the global accrual window (from first patient first consent date to last patient outside of China's consent date). Any patient from China enrolled during the global accrual window will be included
- All Enrolled Subjects: All subjects who signed an informed consent form and were registered into the IVRS
- All Randomized Subjects: All subjects who were randomized to any treatment group
- All Treated Subjects: All subjects who received at least one dose of any study medication
- PK Subjects: All randomized subjects with available serum time-concentration data
- Immunogenicity Subjects: All randomized subjects with available ADA data
- Biomarker Subjects: All randomized subjects with available biomarker data

8.3 Endpoints

8.3.1 Primary Endpoint(s)

OS is defined as the time from randomization to the date of death. A subject who has not died will be censored at last known date alive. OS will be followed continuously while subjects are on the blinded study drug and every 3 months via in-person or phone contact after subjects discontinue the blinded study drug.

8.3.2 Secondary Endpoint(s)

Secondary endpoint of OS comparing nivolumab monotherapy versus placebo is defined similarly to the primary endpoint.

PFS is defined as the time from randomization to the date of the first documented tumor progression (per RECIST 1.1) or death due to any cause. Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on study tumor assessments and did not die will be censored on the date they were randomized. Subjects who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last evaluable tumor assessment prior to initiation of the subsequent anti-cancer therapy. Progression will be assessed every 6 weeks (from the first on-study radiographic assessment) until disease progression is noted.

An OS descriptive analysis will be performed to evaluate nivolumab monotherapy to nivolumab with ipilimumab treatment regimen.

Tumor mutational burden (TMB) is measured using FoundationOne CDx™ (F1CDx) assay, a comprehensive genomic profile (CGP) assay based on baseline tumor tissue. TMB is defined as

the number of somatic, coding, base substitution, and indel mutations per megabase of genome examined.

8.3.3 [redacted]

[redacted]

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Demographics and baseline laboratory results will be summarized by treatment arm as randomized using descriptive statistics for all randomized subjects.

8.4.2 Efficacy Analyses

OS for each of the two experimental arms will be compared to the control group using a two-sided log-rank test stratified by ECOG Performance Status (0 vs 1), Gender (male vs female) and Prophylactic Cranial Irradiation (PCI) following chemotherapy (Yes vs No) (IVRS source) in all randomized subjects. HRs and corresponding two-sided CIs will be estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by the above factors. OS curves, OS medians with 95% CIs, and OS rates at 6, 12 and 18 months with 95% CIs will be estimated using Kaplan-Meier methodology.

BICR-assessed PFS for each of the two experimental arms will be compared to the control group using a two-sided log-rank test stratified by the same stratification factors as in the OS primary analysis. HRs and corresponding two-sided CIs will be estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by the same stratification factors as above. PFS curves, PFS medians with 95% CIs, and PFS rates at 6, 12 and 18 months with 95% CIs will be estimated for each of the three treatment groups using Kaplan-Meier methodology.

Hierarchical procedure will be used to control the overall Type I error rate at 0.05.

The secondary endpoint, OS comparing nivolumab monotherapy vs placebo, will be tested using 2-sided 5% alpha, if superiority of nivolumab in combination with ipilimumab over placebo is demonstrated at the 5% significance level. If superiority in OS of nivolumab monotherapy over placebo is demonstrated, the 5% alpha is passed to test the secondary endpoints of PFS. PFS will be tested hierarchically, starting with comparison of PFS of nivolumab plus ipilimumab with placebo, followed by comparison of PFS of nivolumab monotherapy with placebo. The exploratory endpoint of ORR will be calculated for each treatment group. Exact two-sided 95% CIs for the rates will be computed using the method of Clopper and Pearson for each of the three treatment groups.

Descriptive analyses of OS, PFS, and ORR will be performed to evaluate differences between the two experimental arms, nivolumab combined with ipilimumab and nivolumab monotherapy. These include HRs and medians with corresponding two-sided 95% CIs for OS and PFS, as well as an ORR odds ratio with corresponding 95% CI.

Descriptive analyses will be performed to evaluate the potential of PD-L1 expression and TMB as a predictive biomarker for PFS and OS.

8.4.3 Safety Analyses

Safety analyses will be performed for all treated subjects. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All on-study AEs, drug-related, AEs, SAEs and drug-related SAEs will be tabulated using worst grade per NCI CTCAE v4.0 criteria by system organ class and MedDRA preferred term. The listings by subject will be produced for all deaths, all SAEs, and all AEs leading to discontinuation of blinded study drug. On-study lab parameters including hematology, chemistry, liver function, thyroid function, and renal function will be summarized using worst grade per NCI CTCAE v4.0 criteria.

8.4.4 Pharmacokinetic Analyses

The concentration vs time data obtained in this study may be combined with data from other studies in the clinical development program to develop a population PK model. This model may be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of nivolumab and to determine measures of individual exposure (such as steady-state peak, trough, and time-averaged concentration). Model determined exposures may be used for exposure-response analyses of selected efficacy and safety end points. Results of population PK and exposure-response analyses will be reported separately.

8.4.5 [redacted]

8.4.5.1 Pharmacodynamic Analyses

To assess pharmacodynamic effects in serum obtained from subjects on each treatment arm, summary statistics for biomarkers and their corresponding changes (or percent changes) from baseline will be tabulated by planned study day and in each arm. The time course of biomarker measures will be investigated graphically, if there is indication of meaningful pattern over time, further analysis (eg, by linear mixed model) may be performed to characterize the relationship.

8.4.5.2 Pharmacogenomic Analyses

Pharmacogenomic and Exploratory Analyses

Potential relationships between biomarker data and efficacy or safety endpoints will be investigated as part of an analysis plan aimed at identifying baseline biomarkers that may be used to prospectively identify subjects likely (or not likely) to respond to nivolumab and to identify subjects who may be predisposed to having adverse reactions to treatment. These exploratory predictive biomarker analyses will be completed with biomarkers measured in blood and in tumor samples and will focus primarily as outlined in the exploratory objectives on NPs in select genes associated with immunity or on the expression of PD-1, PD-L1, and PD-L2 proteins in tumor specimens. Similar analyses will be completed with data regarding serum-soluble factors, serum mRNA content, and putative additional analyses to be completed using FFPE tissue.

Associations between biomarkers and efficacy measures will be analyzed on all randomized subjects with available biomarker data. Efficacy measures will include response, PFS, and OS. Demographic and case-history factors will be examined to determine whether stratification or adjustments should be made within the subsequent statistical analyses, and if necessary, the appropriate stratification or adjustment will be made.

Biomarkers will be summarized graphically as they relate to efficacy and safety endpoints, as applicable. Summary statistics will be tabulated. SNP allele frequencies will be summarized. The relationships between binary measures (eg, response) and candidate biomarkers will be investigated using logistic regression. Associations will be summarized in terms of point and interval estimates of hazard ratios, odds ratios, or other statistics, as appropriate for the analyses completed. Models to predict clinical activity based on combinations of biomarkers may also be investigated.

Additional post hoc statistical analyses not specified in the protocol, such as alternative modeling approaches may be completed. All analyses described in this section are based on the availability of the data.

8.4.6 Outcomes Research Analyses

LCSS questionnaire complete rate, defined as the proportion of questionnaires actually received out of the expected number (ie, the number of subjects still on treatment and in follow-up), will be calculated and summarized at each assessment point.

Baseline and change from baseline of the average symptom burden index score at each assessment point will be summarized using descriptive statistics. Subject's overall health state on a visual analog scale (EQ-VAS) at each assessment time point and the difference from baseline will be summarized using descriptive statistics Proportion of subjects reporting problems for the 5 EQ-5D dimensions at each assessment time point will be summarized by level of problem. Summary statistics will be calculated for the population preference-based health state utility score (EQ-5D Index).

8.4.7 Other Analyses

Methodology for exploratory analyses including immunogenicity, other HRQoL assessments (PRO), and healthcare resource utilization is described in the statistical analysis plan.

8.5 Interim Analyses

Not applicable

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if applicable, also by local health authority) 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 relevant approval/favorable opinion(s), the deviation or change will be submitted as soon as possible to:

- IRB/IEC
- Regulatory Authority(ies), if applicable by local regulations per national requirements

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and if applicable, also by local health authority, 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

BMS representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

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 CRFs, 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.

9.1.2.1 Source Documentation

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

9.2 Records

9.2.1 Records Retention

The investigator (or head of the study site in Japan) 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 or designee, whichever is longer. The investigator must contact BMS or designee prior to destroying any records associated with the study.

BMS will notify the investigator (or head of the study site in Japan) 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, study site, IRB). Notice of such transfer will be given in writing to BMS.

9.2.2 Study Drug Records

Records for IP (whether supplied by BMS, its vendors, or the site) must substantiate IP integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

If...	Then...
Supplied by BMS (or its vendors):	Records or logs must comply with applicable regulations and guidelines and should include: • amount received and placed in storage area • amount currently in storage area • label 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 (e.g., 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.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from	The investigator or designee accepts responsibility for documenting traceability and

If...	Then...
the sites stock or commercial supply, or a specialty pharmacy)	study drug integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy.

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

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. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paper or electronic SAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

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

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. Subinvestigators in Japan may not be delegated the CRF approval task. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

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 as appropriate based on 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
Complete Abstinence	Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (eg, calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Women must continue to have pregnancy tests. Acceptable alternate methods of highly or less effective contraception's must be discussed in the event that the subject chooses to forego complete abstinence.

11 LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AIDS	Acquired immunodeficiency syndrome
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AT	aminotransaminases
β-HCG	beta-human chorionic gonadotrophin
BID, bid	bis in die, twice daily
BICR	Blinded independent central review
BMI	body mass index
BMS	Bristol-Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
C	Celsius
Ca++	Calcium
Cavg	average concentration
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
C1-	Chloride
CLcr	creatinine clearance
cm	Centimeter
CNS	Central nervous system
CRC	Clinical Research Center
CRF	Case Report Form, paper or electronic
CTLA-4	Cytotoxic t lymphocyte-associated antigen 4
CYP	cytochrome p-450
D/C	Discontinue

Term	Definition
dL	Deciliter
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
Eg	exempli gratia (for example)
ESR	Expedited Safety Report
FDA	Food and Drug Administration
FISH	Fluorescent in situ hybridization
FSH	follicle stimulating hormone
g	Gram
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GFR	glomerular filtration rate
h	hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCO3-	bicarbonate
HIV	Human Immunodeficiency Virus
HR	heart rate
HRQoL	Health Related Quality of Life
HRT	hormone replacement therapy
ICD	International Classification of Diseases
ICH	International Conference on Harmonization
ie	id est (that is)
IEC	Independent Ethics Committee
IMP	investigational medicinal products
IMAE	Immune-mediated adverse events
IND	Investigational New Drug Exemption

Term	Definition
IRB	Institutional Review Board
IU	International Unit
IU/L	International unit per liter
IU/mL	International unit per milliliter
IVRS	Interactive voice response system
IV	intravenous
K+	potassium
kg	Kilogram
KM	Kaplan-meier
L	Liter
LAM	Lactation amenorrhea method
LCSS	Lung cancer symptom scale
LDH	lactate dehydrogenase
mAB	Monoclonal antibody
mg	Milligram
Mg++	magnesium
Min	Minute
mL	Milliliter
mmHg	millimeters of mercury
MTD	maximum tolerated dose
µg	Microgram
N	number of subjects or observations
Na+	Sodium
N/A	not applicable
NE	Not evaluable
Ng	Nanogram
NCCN	National Comprehensive Cancer Network
NIMP	non-investigational medicinal products
ORR	Overall response rate
OS	Overall survival

Term	Definition
PD	Progressive disease
PD	Pharmacodynamics
PD-1	Programmed Death-1
PD-L1	Programmed death-ligand 1
PD-L2	Programmed death-ligand 2
PFS	progression-free survival
PR	Partial response
PK	Pharmacokinetics
PT	prothrombin time
RCC	Renal cell carcinoma
RECIST 1.1	Resonse evaluation criteria in solid tumors version 1.1
RBC	red blood cell
SAE	serious adverse event
SD	standard deviation
SD	Stable disease
SOP	Standard Operating Procedures
t	Temperature
T	Time
TAO	Trial Access Online, the BMS implementation of an EDC capability
T-HALF	Half life
TID, tid	ter in die, three times a day
TILs	Tumor infiltrating lymphocytes
TSH	Thyroid stimulating hormone
Tmax, TMAX	time of maximum observed concentration
ULN	Upper limit of normal
VAS	Visual analog scale
WBC	white blood cell
WOCBP	women of childbearing potential

APPENDIX 3 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS GUIDELINES (VERSION 1.1) WITH BMS MODIFICATIONS

1 EVALUATION OF LESIONS

Solid tumors will be evaluated using Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1) guideline with BMS modifications. (Eisenhauer EA et al. Eur J Cancer 2009; 45: 228-47)

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows:

1.1 Measurable

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

10 mm by CT/MRI scan (scan slice thickness no greater than 5 mm), or ≥ 2x slice thickness if greater than 5mm.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT/MRI scan (scan slice thickness recommended to be no greater than 5 mm).

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/MRI scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

Note: Lesions on X-Ray are not to be selected as Target or Non-Target Lesions.

1.2 Non-Measurable

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

Note: Lesions on X-Ray are not to be selected as Target or Non-Target Lesions.

1.3 Special considerations regarding lesion measurability

1.3.1 Bone lesions

- Bone scan, PET scan and 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.

1.4 Baseline Documentation Of 'Target' And 'Non-Target' Lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Note: A maximum of two lesions can be selected per organ system. For example, a maximum of two lung lesions can be selected (selected from one lung or one lesion from each). A maximum of two lymph nodes can be selected at baseline, as the lymphatic system is considered one organ.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

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 above, 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.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2. RESPONSE CRITERIA

2.1 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.
- **Not Evaluable (NE):** If one or more target lesions cannot be measured or adequately assessed as either fully resolved or too small to measure (due to missing or poor quality images), and the sum of diameters of the remaining measured target lesions (if any) has not increased sufficiently to meet Progressive Disease as defined above.

2.1.1 Special Notes on the Assessment of Target Lesions

2.1.1.1 Lymph nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 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. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

2.1.1.2 Target lesions that become 'too small to measure'

While on study, 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). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. 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 as the reference diameter. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded

by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is 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). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

2.1.1.3 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. Similarly, as lesions coalesce, a plane between them may be 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'.

2.2 Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group 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 (< 10mm short axis).
- **Non-CR/Non-PD:** Persistence of one or more non-target lesion(s)
- **Progressive Disease (PD):** Unequivocal progression of existing non-target lesions.

2.2.1 Special Notes on Assessment of Progression of Non-Target Disease

The concept of progression of non-target disease requires additional explanation as follows:

2.2.1.1 When the patient also has measurable disease

In this setting, 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. Pleural effusions, pericardial effusions and ascites will not be followed as target or non-target lesions and will not contribute to response or progression. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

2.2.1.2 When the patient has only non-measurable disease

This circumstance arises in some trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include, an increase in lymphangitic disease from localized to widespread, or may be described as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

2.2.2 New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, 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 pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

NOTE: Fluid collections (pleural effusions, pericardial effusions, and ascites) will not be considered new lesions and will not contribute to response or progression. In the event a new fluid collection is seen on a post-baseline imaging exam, a comment may be made, but the appearance of a new fluid collection alone should not result in an assessment of Progressive Disease (PD). 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 patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline. A lesion identified on Chest X-Ray that was not present in prior CT can be considered a new lesion and will result in Progressive Disease (PD).

If a new lesion is equivocal, for example because of its small size, continued 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. While FDG-

PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
2. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

2.3 Response Assessment

2.3.1 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until disease progression or the last response recorded, taking into account any requirement for confirmation and censoring rules regarding subsequent therapy. The patient'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. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement.

2.3.2 Time Point Response

At each protocol specified time point, a response assessment occurs. Table 2.3.2-1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore non-target) disease only, Table 2.3.2-2 is to be used.

Table 2.3.2-1: Time Point Response: Patients 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

Table 2.3.2-1: Time Point Response: Patients With Target (± Non-Target) Disease			
Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease and NE = inevaluable

Table 2.3.2-2: Time Point Response: Patients with Non-target Disease Only		
Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR = complete response, PD = progressive disease and NE = inevaluable		

[a] Non-CR/non-PD is preferred over SD for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

2.3.3 Best Overall Response

Best response determination of complete or partial response requires confirmation: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point of ≥ 4 weeks (28 days) later. In this circumstance, the best overall response can be interpreted as in Table 2.3.3-1. When SD is believed to be best response, it must meet the protocol specified minimum time from the date of first treatment or randomization date.

For example, if the first scheduled follow-up imaging visit is Week 6 (± 7 days) for a particular protocol, a Best Response of SD can only be made after the subject is on-study for a minimum of 6 weeks (42 days) minus 7 days, for an absolute minimum time on-study of 35 days from the reference start date (reference date is considered Day 1 on study). If the subject is not on-study for at least this amount of time, any tumor assessment indicating stable disease before this time period will have a Best Response of NE unless PD is identified.

Special note on response assessment: When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

Table 2.3.3-1: Best Overall Response (Confirmation of CR and PR Required)		
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**Best Overall Response**
CR	CR	CR
CR	PR	SD, PD OR PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE
CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable		

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

2.3.4 Confirmation Scans

Verification of Response: To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive or subsequent repeat assessments that should be performed no less than 28 days after the criteria for response are first met. Subsequent documentation of a CR may provide confirmation of a previously identified CR even with an intervening NE or PR (eg, CR NE CR or CR PR CR). Subsequent documentation of a PR may provide confirmation of a previously identified PR even with an intervening NE or SD (eg, PR NE PR or PR SD PR). However, only one (1) intervening time point will be allowed between PR/CRs for confirmation.

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 to not have progressive disease.

[redacted]