Protocol Number: CA209743
IND Number: 131,841
Ex-US: Non-IND
EUDRACT Number 2016-001859-43
Date: 25-May-2016
Revised Date: 25-Apr-2019

Clinical Protocol CA209743

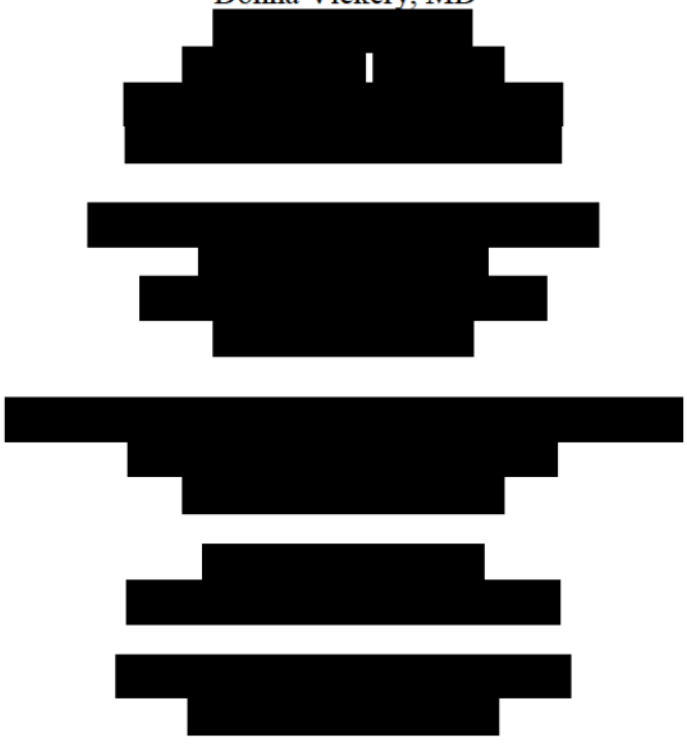
A Phase III, Randomized, Open Label Trial of Nivolumab in combination with Ipilimumab versus Pemetrexed with Cisplatin or Carboplatin as First Line Therapy in unresectable Pleural Mesothelioma

CheckMate 743: **CHECK**point pathway and nivolu**MA**b clinical **T**rial **E**valuation **743**

Revised Protocol Number: 02
Incorporates Administrative Letters 06 and 07

Study Director/Medical Monitor

Donna Vickery, 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 02	25-Apr-2019	• Change of progression free survival from co-primary to secondary endpoint and removal of hierarchical testing of secondary endpoints • Update of the statistical assumptions for the primary analysis in light of emerging data from external studies • Clarification of BICR assessed progression • Language updated for vaccines for prohibited treatment • Updated outcome assessments • Updated adverse event definitions • Updated Appendix 2 [redacted] • Updated Appendix 3 Women of Child Bearing Potential Definition and Methods of Contraception
Administrative Letter 07	10-Jul-2018	Clarified dilution instructions for nivolumab to align with Investigator Brochure
Administrative Letter 06	27-Feb-2018	Clarified weight-based dosing calculation requirements for nivolumab and ipilimumab
Revised Protocol 01	13-Oct-2017	• Addition of 2 year maximum treatment duration • Clarification of tissue submission requirements • Mesothelioma disease measurement updated • Radiographic assessment criteria of modified RECIT and RECIST 1.1 updated and imaging assessments were updated • Study design, assessments, and dosing schedule were clarified for consistency • Inclusion and exclusion criteria were updated • Language updated for prohibited treatments, treatment schedule, • Dose delay criteria for study treatment and discontinuation criteria were updated as per program standards [redacted] • Typographical and formatting errors were corrected and wording updated for consistency
Administrative Letter 05	06-Mar-2017	Updated study personnel and clarified treatment windows, pretreatment windows, and pathological tissue requirements. Chemotherapy treatment was updated for administration according to label and/or local policy and weight-based dosing calculations.
Administrative Letter 04	06-Dec-2016	Updated study personnel
Administrative Letter 03	27-Sep-2016	Prohibitions for the additional research collection and retention was clarified.
Administrative Letter 02	17-Aug-2016	Updated IND Number and updated chemotherapy infusion duration
Administrative Letter 01	20-Jul-2016	Updated title page information

Document	Date of Issue	Summary of Change
Original Protocol	25-May-2016	Not applicable

[redacted]

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 02

Section Number & Title	Description of Change	[redacted]
Synopsis Objectives, Endpoints Section 1.3.1 Primary Objective Section 1.3.2 Secondary Objectives [redacted] Section 3.1 Study Design and Duration Section 5.5 Efficacy Assessments	• PFS moved to secondary endpoints. [redacted]	[redacted]
Synopsis Schema Figure 3.1-1 CA209743 Study Design Schematic	Updated schema	[redacted]
Synopsis Sample size Section 8.1 Sample size determination	• Updated the alpha level for OS analysis, median OS for control Arm B, delayed period of treatment effect, accrual rate and required OS event numbers. • Removed the PFS section.	[redacted]
Section 1.1.2.1 [redacted]	[redacted]	[redacted]
Section 1.2 Research Hypothesis	Removed PFS from the research hypothesis	[redacted]
Section 3.4.1 Prohibited and/or Restricted Treatments	Prohibited any live / attenuated vaccine during treatment and until 100 days post last dose.	[redacted]
Section 4.5.1.1 Nivolumab plus Ipilimumab Table 5.1-2 On Treatment Procedural Outline	Language for dosing calculations was updated.	[redacted]
Section 4.5.2.1 Dose Delay Criteria for Nivolumab plus Ipilimumab Section 4.5.4.1 Criteria to Resume Nivolumab Dosing	Language regarding dose modifications for amylase or lipase abnormalities were removed.	[redacted]

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 02

Section Number & Title	Description of Change	[redacted]
Section 4.5.5.2 Ipilimumab Dose Discontinuation		
Section 4.6 Treatment Beyond Disease Progression (Arm A only)	Language modified to require BMS Medical Monitor approval to treat beyond initial investigator-assessed and independent central review confirmed progression.	
Synopsis Table 5.1-2 On Treatment Procedural Outline Table 5.1-3: Follow up period (CA209743): Both treatment arms	Added Blinded Independent Central Review (BICR) confirmation of disease progression throughout the protocol.	
Table 5.1-2 On Treatment Procedural Outline Table 5.1-3 Follow up period (CA209743): Both treatment arms Section 8.4.6 Outcomes Research Analyses		
Section 6 Adverse Events	Adverse events definitions were updated.	
Section 6.3 Laboratory Test Result Abnormalities	Section 6.3 was removed	
Section 6.5 Overdose	Section 6.5 was removed.	
Section 8.1 Sample size determination Section 8.3 Endpoints Section 8.4.2 Efficacy Analyses	• Updated the alpha level for OS analysis, median OS for control Arm B, delayed period of treatment effect, accrual rate and required OS event numbers. • Removed the PFS section. • Changed PFS from a primary endpoint to a secondary endpoint.	

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	[redacted]
	[redacted] • Removed PFS analyses from the primary endpoints analyses, removed the hierarchical testing approach, removed the comparison analyses between two arms for ORR, DOR and PFS.	[redacted]
Section 8.5 Interim Analysis	Updated the required OS event numbers for interim and final OS analysis	[redacted]
Appendix 2 [redacted]	Appendix updated	[redacted]
Appendix 3 [redacted]	Appendix updated	[redacted]
Document History	Updated and corrected document history	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

SYNOPSIS

Clinical Protocol CA209743

Protocol Title: A Phase III, Randomized, Open Label Trial of Nivolumab in combination with Ipilimumab versus Pemetrexed with Cisplatin or Carboplatin as First Line Therapy in unresectable Pleural Mesothelioma

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

Subjects randomized to either Arm A: nivolumab combined with ipilimumab Arm, or Arm B: Control Arm.

- Arm A: nivolumab administered IV over 30 minutes at 3 mg/kg every 2 weeks combined with ipilimumab administered IV over 30 minutes at 1 mg/kg every 6 weeks until progression, unacceptable toxicity, or other reasons specified in the protocol
- Arm B: pemetrexed (500 mg/m2) with either cisplatin (75 mg/m2) or carboplatin (AUC 5); on day 1 of every 21 days for 6 cycles or until disease progression or unacceptable toxicity.

Study Phase: III

Research Hypothesis: In patients with untreated unresectable pleural mesothelioma, the administration of nivolumab in combination with ipilimumab as first line treatment compared to pemetrexed plus cisplatin or carboplatin regimen will lead to increased overall survival (OS).

Objectives:

Primary Objective:

- To compare overall survival (OS) of nivolumab combined with ipilimumab to pemetrexed plus cisplatin or carboplatin regimen as first line treatment in patients with unresectable malignant pleural mesothelioma.

Secondary Objectives:

- To assess the objective response rate (ORR) as determined by blinded independent central review (BICR), of nivolumab combined with ipilimumab and pemetrexed plus cisplatin or carboplatin as first line treatment in patients with unresectable malignant pleural mesothelioma.
- To assess the Disease Control Rate (DCR) as determined by BICR, of nivolumab combined with ipilimumab and pemetrexed plus cisplatin or carboplatin as first line treatment in patients with unresectable malignant pleural mesothelioma.
- To assess progression free survival (PFS) as determined by BICR, of nivolumab combined with ipilimumab and pemetrexed plus cisplatin or carboplatin as first line treatment in patients with unresectable malignant pleural mesothelioma.
- To evaluate whether PD-L1 expression is a predictive biomarker for ORR, PFS, and OS.

[redacted]

[redacted]

Study Design: This is an open label, randomized, Phase 3 study in adult (≥ 18 years) male and female subjects, as a first line therapy for diagnosed unresectable malignant pleural mesothelioma.

Subjects in each arm will be stratified by:

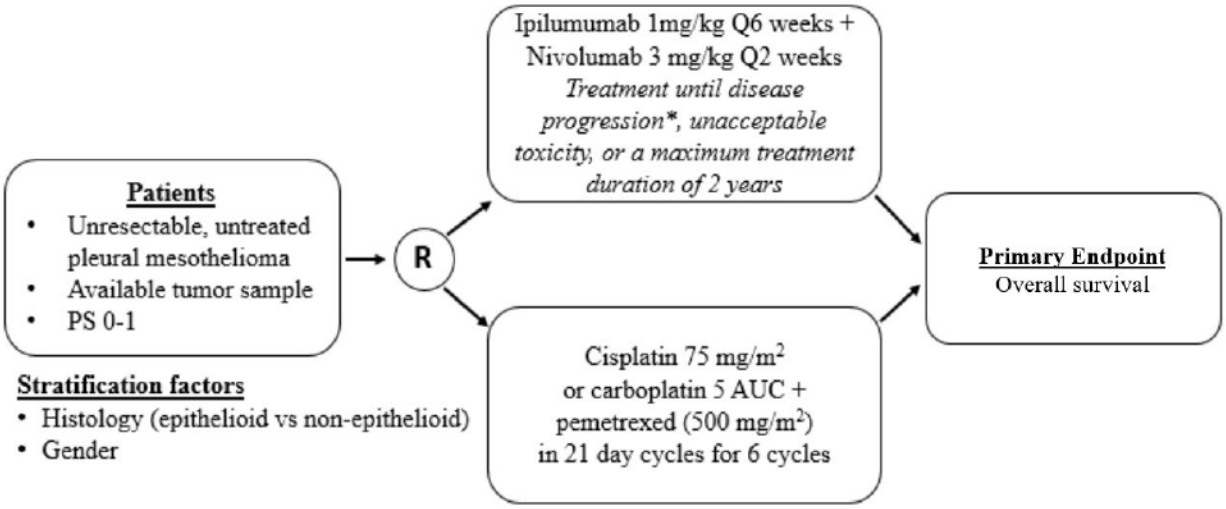
- histology: Epithelioid vs non-epithelioid
- gender: male or female

Subjects will be randomized in 1:1 and treated with one of the following open-label treatments:

- Arm A: nivolumab administered IV over 30 minutes at 3 mg/kg every 2 weeks combined with ipilimumab administered IV over 30 minutes at 1 mg/kg every 6 weeks until progression, unacceptable toxicity, or other reasons specified in the protocol and for a maximum treatment duration of 2 years,. Treatment beyond initial investigator-assessed and BICR confirmed progression according to adapted modified RECIST (m-RECIST) and/or RECIST 1.1 defined progression is permitted if the subject has investigator assessed clinical benefit and is tolerating nivolumab, as specified in Section 4.6
- Arm B: pemetrexed plus cisplatin or carboplatin chemotherapy administered on day 1 of every 21 days for up 6 cycles. Chemotherapy treatment will continue until disease progression, unacceptable toxicity, or completion of 6 cycles, whichever comes first.

On-study tumor assessments will begin at Week 6 post randomization (± 7 days) and be performed every 6 weeks (± 7 days) for the first 12 months and every 12 weeks (± 7 days) thereafter, or until disease progression is confirmed, whichever occurs first.

Enrollment will end after approximately 600 subjects have been randomized.



Treatment beyond initial investigator-assessed and BICR-confirmed progression according to adapted m-RECIST and/or RECIST 1.1 criteria may be allowed. See Section 4.6.

Study Population: Subjects must meet all eligibility criteria specified in Section 3.3 of the protocol, including the following:

Key Inclusion Criteria

- Male and female subjects (≥ 18 years of age).
- Histologically proven diagnosis of MPM, thoracoscopy is highly recommended.
- Advanced unresectable disease that is not amenable to therapy with curative intent (surgery with or without chemotherapy). Subjects that refuse potentially curative surgery are ineligible

- Available (archival and/or fresh) pathological samples for centralized PD-L1 IHC testing during the screening period. Subjects cannot be randomized until the tumor tissue for PD-L1 testing has been received at the Central Lab, however, the result of the testing is not required prior to randomization. Subjects can initiate therapy before the result of PD-L1 testing is available.
- Prior palliative radiotherapy is acceptable, but at least 14 days must have passed since the administration of the radiotherapy and all signs of toxicity must have remitted.
- ECOG Performance Status of 0-1 (Appendix 1).
- Measurable disease, defined as at least 1 lesion measured in up to two positions at three separate levels on transverse cuts of CT scan that is suitable for repeated assessment using adapted modified Response Evaluation Criteria in Solid Tumors [m-RECIST] for pleural mesothelioma
- Adequate hematological, renal and hepatic functions

Key Exclusion Criteria

- Primitive peritoneal, pericardial and tunica vaginalis testis mesotheliomas
- Brain metastasis, except if surgically resected or treated with stereotaxic radiotherapy with no evolution within the 3 months before inclusion, and asymptomatic. In addition, subjects must be either off corticosteroids, or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent) for at least 2 weeks prior to randomization,
- Prior treatment with adjuvant or neoadjuvant chemotherapy; radical pleuropneumonectomy with or without intensity modulated radiotherapy, or non-palliative RT
- Prior intraoperative or intracavitary chemotherapy for pleural mesothelioma
- Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.
- History of chronic inflammatory or autoimmune disease
- Concurrent or prior malignancy requiring or anticipated to require concurrent intervention
- Subjects with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity.

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

Study Drug for CA209743		
Medication	**Potency**	**IP/Non-IP**
Nivolumab	10 mg/ml	IMP
Ipilimumab	5 mg/ml	IMP
Pemetrexed	25 mg/ml	IMP
Pemetrexed (China)	Varies per market product	IMP
Cisplatin	1 mg/ml	IMP
Cisplatin (China)	Varies per market product	IMP
Carboplatin	10 mg/ml	IMP
Carboplatin (China)	Varies per market product	IMP

Study Assessments: This study will consist of three phases: screening, treatment, and follow-up.

Screening Phase

- Begins by establishing the subject's initial eligibility and signing of the informed consent (ICF).
- Subject is enrolled using the Interactive Web Response System (IWRS).
- Tumor tissue (archival or recent tumor biopsy) must be submitted by the site to a third-party vendor for determination of PD-L1 status. An email communication will be sent by the third party vendor to site for confirmation upon receiving tumor tissue. Subjects can initiate therapy before the result of PD-L1 IHC testing.
- Subject is assessed for study eligibility

All screening assessments and procedures must be performed within 28 days prior to treatment, unless otherwise specified.

Treatment Phase

- The treatment begins with the call to the IWRS to randomize the patient.
- Treatment should begin within 3 calendar days of randomization.

Arm A:

- nivolumab 3 mg/kg IV will be administered every 2 weeks.
- ipilimumab 1 mg/kg IV will be administered every 6 weeks on the same day as the administration of nivolumab.
- On the day of infusion of nivolumab and ipilimumab, nivolumab is to be administered first. The second infusion will always be ipilimumab, and will start at least 30 minutes after completion of the nivolumab infusion.

Nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks will be continued until progression of disease, discontinuation due to toxicity, withdrawal of consent, a maximum treatment duration of 2 years, or study closure. Subjects may discontinue only ipilimumab and continue treatment with nivolumab if certain circumstances are met (outlined in full protocol).

Arm B:

- Pemetrexed (500 mg/m2) plus cisplatin (75 mg per meter of BSA) or carboplatin (AUC of 5 mg per milliliter per minute) all on day 1, every 21 days for 6 cycles or until disease progression or unacceptable toxicity. The use of cisplatin is preferred, however or carboplatin may be used at the discretion on the investigator, and the reason for using carboplatin instead of cisplatin must be reported in the CRF.

Overall survival is the primary endpoint of the study. Overall survival is defined as the time from randomization to the date of death. Subjects will be assessed for response by CT scans beginning at 6 weeks (± 7 days) after randomization and continuing every 6 weeks (± 7 days) for 12 months and every 12 weeks (± 7 days) thereafter, until progression is BICR confirmed. In the absence of progression after 12 months, tumor assessment should occur every 12 weeks (± 1 week) until disease progression is BICR confirmed. A subject who has not died will be censored at last known alive date. OS will be followed continuously while subjects are on the study drugs and every 3 months via in-person or phone contact after subjects discontinue the study drugs. All randomized subjects will be evaluated.

Statistical Considerations:

Sample Size:

Approximately 600 subjects were to be randomized to two treatment groups in a 1:1 ratio, with 606 subjects actually randomized. The sample size is based on the comparison of the primary endpoint of OS between treatment groups, with two-sided overall alpha of 0.05 for OS.

For OS, approximately 473 events (ie, deaths), observed among the 606 randomized subjects, provides 90% power to detect an average hazard ratio (HR) of 0.72 with a type 1 error of 0.05 (two-sided). There is one planned interim analysis of OS for superiority at approximately 85% of total events, ie, 403 deaths. It is estimated that it will take approximately 38/56 months to observe the required number of events for the interim/final OS analysis.

The above sample size calculation were based on a simulation model incorporating aspects of immuno-oncology therapies like delayed separation and long term benefit (cure rate) using EAST 6.

Endpoints:

Primary Endpoint:

- Primary endpoints of OS

Secondary Endpoints:

- Objective response rate (best overall response [BOR] is either a complete response [CR] or partial response [PR] per adapted m-RECIST and/or RECIST 1.1 criteria) assessed by BICR
- Disease control rate (BOR is CR, PR, or stable disease [SD]) assessed by BICR
- PFS assessed by BICR
- ORR, PFS, and OS by PD-L1 expression level

[redacted]

Analyses:

Demographics and Baseline Characteristics:

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

Efficacy Analyses:

Efficacy analyses will be performed using all randomized subjects by treatment group as randomized.

The distribution of OS will be compared in two randomized arms at the interim and final analysis via a two-sided, log-rank test stratified by histology and gender with an overall significance level of 0.05. A group sequential testing procedure will be applied to OS to control the overall type I error for interim and final analyses.

Hazard ratio, median, and survival rate at different time points will be estimated for both OS and PFS.

Objective response rate, disease control rate, and the distribution of PFS assessed by BICR will be estimated. Time to response and the duration of response will also be evaluated.

Safety Analyses:

The safety analysis will be performed in all treated subjects. Descriptive statistics of safety will be presented using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 by treatment arm.

[redacted]

[redacted]

Interim Analyses:

A formal interim analysis for the OS is planned after 403 deaths have been observed, which are expected to occur approximately 38 months after study initiation. At the time of the interim analysis, the data monitoring committee (DMC) will review efficacy and safety data as will be specified in the DMC charter. This formal comparison of OS will allow for early stopping for superiority. In addition to the formal planned interim analysis for OS, the DMC will have access to periodic unblinded interim reports of efficacy and safety to allow a risk/benefit assessment with formal test.

TABLE OF CONTENTS

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1.2 Research Hypothesis

In subjects with untreated unresectable malignant pleural mesothelioma, the administration of nivolumab in combination with ipilimumab as first line treatment compared to pemetrexed plus cisplatin or carboplatin regimen will lead to increased overall survival (OS).

1.3 Objectives(s)

1.3.1 Primary Objective

- To compare overall survival (OS) of nivolumab combined with ipilimumab to pemetrexed plus cisplatin or carboplatin regimen as first line treatment in subjects with unresectable malignant pleural mesothelioma.

1.3.2 Secondary Objectives

- To assess the objective response rate (ORR) as determined by Blinded Independent Committee Review (BICR), of nivolumab combined with ipilimumab and pemetrexed plus cisplatin or carboplatin as first line treatment in subjects with unresectable pleural mesothelioma.
- To assess the Disease Control Rate (DCR) as determined by BICR, of nivolumab combined with ipilimumab to pemetrexed plus cisplatin or carboplatin as first line treatment in subjects with unresectable malignant pleural mesothelioma.
- To assess progression-free survival (PFS) as determined by BICR of nivolumab combined with ipilimumab and pemetrexed plus cisplatin or carboplatin as first line treatment in subjects with unresectable malignant pleural mesothelioma.
- To evaluate whether PD-L1 expression is a predictive biomarker for ORR, PFS, and OS.

[redacted]

[redacted]

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 Harmonization (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 Sponsor or designee 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, Sponsor or designee 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.

Sponsor or designee 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:

- 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.
- Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
- 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.
- 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.

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.

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

Protocol CA209743 is a randomized (1:1), open-label, Phase 3 trial in subjects ≥ 18 years old with untreated unresectable MPM, evaluating nivolumab combined with ipilimumab versus pemetrexed plus cisplatin or carboplatin as a first line treatment.

Subjects will undergo screening evaluations to determine eligibility within 28 days prior to first treatment. It is expected that 800 subjects will be enrolled, and approximately **600** subjects will be randomized.

Randomization will be stratified according to tumor histology: epithelioid vs sarcomatoid or mixed histology subtypes and to gender: male vs female. Tumor sample for PD-L1 status assessment is required prior to randomization, but results are not needed for randomization.

Subjects will be treated with one of the following:

- Arm A (nivolumab/ipilimumab Combo): nivolumab 3 mg/kg IV every 2 weeks + ipilimumab 1 mg/kg IV every 6 weeks until disease progression, unacceptable toxicity, , or a maximum treatment duration of 2 years.
- Arm B (Control Arm): pemetrexed 500 mg/m2 plus cisplatin 75 mg/m2 or carboplatin (AUC of 5 mg per milliliter per minute), on day 1 of a 21-days cycle for 6 cycles or until disease progression or unacceptable toxicity. The choice of cisplatin is preferred, however the use of carboplatin is at the discretion of the investigator, and the reason for using carboplatin must be documented in the CRF. Arm B dose calculations will be administered according to label and/or local policy in terms of infusion schema (including but not limited to hydration protocols). Vitamins B12 and B9 supplementation and dexamethasone premedication are required for all subjects receiving pemetrexed. Dexamethasone can be given as IV infusion on the day of treatment as required by pemetrexed label and/or local SOC.

Comparator selection

In CA209743 study, nivolumab combined with ipilimumab will be compared to the widely approved standard of care: pemetrexed plus cisplatin. Carboplatin will be allowed instead of cisplatin, as per the investigator assessment, based on published data from an expanded access program on 1,704 chemo-naive subjects with MPM confirmed similar response rates, time-to-progression and one-year survival using pemetrexed plus carboplatin and pemetrexed plus cisplatin.[14]

Although, bevacizumab combined to pemetrexed and cisplatin has improved OS and PFS in chemo-naive MPM subjects, compared to pemetrexed plus cisplatin, in one randomized single country study[15], bevacizumab was not considered as part of the control arm for the current study, given the following:

- This strategy is not approved by any regulatory agency,
- Patients over 75 years of age were excluded from this study,

- Absence of any clinical data from comparative studies, suggesting any superiority of bevacizumab combined with carboplatin and pemetrexed over chemotherapy,

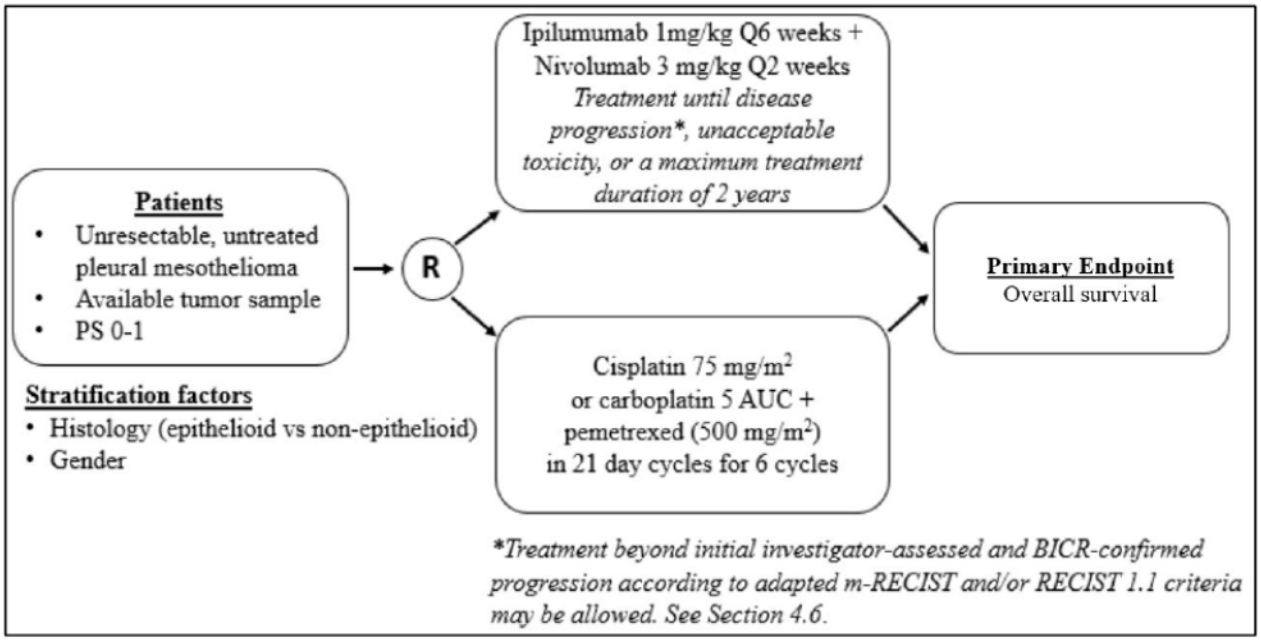
All this, in view of the previous negative trial of bevacizumab added to cisplatin and gemcitabine, showing that the addition of bevacizumab to gemcitabine/cisplatin in this trial did not significantly improve PFS or OS in subjects with advanced malignant mesothelioma.[47]

Study primary endpoints

Tumor measurements used in response rate determinations can be imprecise in locations where there is a lack of demarcated margins such as MPM. Therefore, overall survival is the optimal primary endpoint for this study.

The study will end when analysis of overall survival is complete. The duration of study will be approximately 59 months. The study design schematic is presented in Figure 3.1-1.

Figure 3.1-1: CA209743 Study Design Schematic



This study will consist of three phases: screening, treatment, and follow-up.

Screening Phase

- Begins by establishing the subject's initial eligibility and signing of the informed consent (ICF).
- Subject is enrolled using the Interactive Web Response System (IWRS).
- Tumor tissue (archival or recent tumor biopsy within 6 months of randomization) must be submitted by the site to a third-party vendor for determination of PD-L1 status. An email communication will be sent by the third party vendor to site for confirming receipt of tumor tissue. Subjects can initiate therapy before the result of PD-L1 IHC testing.
- Subject is assessed for study eligibility
- All screening assessments and procedures must be performed according to Table 5.1-1.

Treatment Phase

- The treatment begins with the call to the IWRS to randomize the subject.
- Treatment should begin within 3 calendar days of randomization.

Arm A (Nivolumab/Ipilimumab Combination):

Note: 1 cycle= 6 weeks

- Nivolumab 3 mg/kg IV will be administered every 2 weeks.
- Ipilimumab 1 mg/kg IV will be administered every 6 weeks on the same day as the administration of nivolumab.
- On the day of infusion of both nivolumab and ipilimumab, nivolumab is to be administered first. The infusion time for nivolumab will be 30 minutes. Ipilimumab will always be infused after nivolumab and will start at least 30 minutes after the completion of the nivolumab infusion. The infusion time for ipilimumab will be 30 minutes.
- Nivolumab 3 mg/kg Q2 weeks and ipilimumab 1 mg/kg Q6 weeks will be continued until the progression of disease, discontinuation due to toxicity, withdrawal of consent, or study closure. As per Section 4.5.5.2 Subjects may discontinue only ipilimumab and continue treatment with nivolumab if requirements of section Section 4.5.4 are met.
- Treatment beyond initial investigator-assessed and BICR confirmed progression as defined by adapted m-RECIST for pleural mesothelioma and RECIST 1.1, is permitted if the subject has investigator-assessed clinical benefit and is tolerating treatment, as per Section 4.6.

Arm B (Control Arm):

- Pemetrexed (500 mg/m2) plus cisplatin (75 mg per meter of BSA) or carboplatin (AUC of 5 mg per milliliter per minute) all on day 1 of 21 days cycle, for 6 cycles or until disease progression and unacceptable toxicity. The use of cisplatin is preferred, however carboplatin may be used at the discretion of the investigator, and the reason for using carboplatin instead of cisplatin must be reported in the CRF.

Premedication Regimen:

1. Vitamin Supplementation:

   Prior to treatment, and in order to reduce the risk of hematologic and gastrointestinal toxicity due to pemetrexed, .supplementation with oral folic acid and intramuscular vitamin B12 is required and has to be started 1 week prior to the first day of therapy. After randomization, this premedication will be discontinued in patients randomized to Arm A (nivolumab and ipilimumab)

   – Oral folic acid 350 to 1000 µg daily should be given starting 1 week prior to Cycle 1 day 1, with at least 5 doses of folic acid administered in the 7 days prior to the first dose. For patients randomized to Arm B, oral folic acid should be continued daily throughout treatment with pemetrexed, and for 21 days after the last dose of pemetrexed (Day 105).

   – Intramuscular (IM) injection of vitamin B12 1000 µg should be given approximately one week prior to Cycle 1 day 1. For patients randomized to Arm B, repeat intramuscular vitamin B12 1000 µg during treatment as per local policy.

2. Corticosteroids:

On Arm B only, the recommendation is to administer dexamethasone 4 mg orally twice daily the day before, the day of, and the day after pemetrexed administration. Sites may follow local policy for corticosteroid administration.

- Vitamin B12 and Dexamethasone/corticosteroids should be administered as per local policy. Dexamethasone can be given as IV infusion on the day of treatment.
- Study assessments are to be collected as outlined in 5.1.
- Upon completion of dosing, subjects will enter the Follow-up Phase.

Follow-up Phase:

The post-treatment follow-up begins when the decision is made to discontinue a subject from all treatment in Arm A, or when up to 6 cycles of chemotherapy are completed on Arm B.

Subjects who discontinue treatment for reasons other than disease progression will continue to have tumor assessments (if clinically feasible) according to the schedule in Table 5.1-3 until progression is confirmed by BICR.

At the time of investigator-assessed radiographic progression per adapted m-RECIST and/or RECIST 1.1 criteria for assessment of response, sites must submit CT scan for blinded independent committee review. Disease progression must be confirmed by BICR prior to discontinuation of treatment. Subjects will be followed for drug-related toxicities until these toxicities resolve, return to baseline or are deemed irreversible. All adverse events will be documented for a minimum of 100 days after the last dose of study medication.

After completion of the first two follow-up visits, subjects will be followed every 3 months for survival. Survival Follow-up visits may be performed by phone contact or office visit. BMS may request that survival data be collected on all treated subjects outside of the protocol defined window. At that time of this request, each subject will be contacted to determine their survival status unless the subject had withdrawn consent for all contact.

3.2 Post Study Access to Therapy

At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study drug. 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 (28 days screening period from enrollment to first treatment):

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, and laboratory testing.

2. Target Population

a) Histologically proven diagnosis of malignant pleural mesothelioma (MPM) with determination of epithelioid vs non-epithelioid histology, thoracoscopy is highly recommended.

b) Must have advanced unresectable disease that is not amenable to therapy with curative intent (surgery with or without chemotherapy). Subjects that refuse potentially curative surgery are ineligible.

c) Available (archival and/or fresh) pathological samples for centralized PD-L1 IHC testing. Subjects cannot be randomized until the tumor sample has been received at the central laboratory, but testing result is not required prior to randomization.

d) Prior palliative radiotherapy is acceptable, however at least 14 days must have passed prior to first treatment, and all signs of toxicity must have remitted. Prior prophylactic radiotherapy to a pleurodesis drainage tract or biopsy site is allowed

e) Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-1 (Appendix 1).

f) Measurable disease is defined as

i) Mesothelioma tumor thickness perpendicular to the chest wall or mediastinum, that can be measured in up to two positions at three separate levels on transverse cuts of CT scan (cuts must be at least 10 mm apart), for a total of up to 6 measurements. Each single tumor measurement must be at least 10 mm to qualify as measurable disease and contribute to the sum that defines the pleural measurement. See Appendix 4.

ii) Non-pleural metastatic target lesions measured uni-dimensionally as per RECIST 1.1 criteria. See Appendix 4.

iii) Patients who present without pleural lesions that can be considered measurable, but with metastatic lesions meeting criteria for target lesion by RECIST 1.1 criteria may be considered for inclusion after consultation with the Medical Monitor.

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.

h) Subjects with a history of pleurodesis are allowed on study.

3. Age and Reproductive Status

a) Males and Females, ages ≥ 18 years, 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 treatment start.

c) Women must not be breastfeeding.

d) Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception from the time of enrollment for the duration of treatment with:

i) ARM A: for a period of 30 days (duration of ovulatory cycle) plus the time required for the investigational drug to undergo five half-lives. The terminal half-life of nivolumab is up to 25 days. WOCBP randomized to receive nivolumab plus ipilimumab should use an adequate method to avoid pregnancy for 23 weeks (30 days plus the time required for nivolumab to undergo five half-lives) after the last dose of investigational drug.

ii) ARM B: chemotherapy plus 5-half-lives of chemotherapy plus 30 days (duration of ovulatory cycle) for a total of 30 days post treatment completion or a duration specified by the local labels of the chemotherapy drugs received, whichever is longer.

e) Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with:

i) ARM A: nivolumab plus 5 half-lives of nivolumab plus 90 days (duration of sperm turnover) for a total of 31 weeks post treatment completion.

ii) Arm B: chemotherapy plus 5 half-lives of chemotherapy plus 90 days (duration of sperm turnover) for a total of 90 days post treatment completion or a duration specified by the local labels of the chemotherapy drugs received, whichever is longer (for subjects treated in the control arm).

f) Azoospermic males are exempt from contraceptive requirements. WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, and still must 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. At minimum, subjects must agree to use one highly effective method of contraception as described in Appendix 3.

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Primitive peritoneal, pericardial, testis or tunica vaginalis mesothelioma.

b) Brain metastasis, except if surgically resected or treated with stereotaxic radiotherapy with no evolution within the 3 months before inclusion. In addition, subjects must be asymptomatic and either off corticosteroids, or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent) for at least 2 weeks prior to first treatment.

c) Undetermined histology of epithelioid vs non-epithelioid status

2. Medical History and Concurrent Diseases

a) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.

b) Prior therapy for MPM (including chemotherapy [adjuvant, neoadjuvant], radical pleuropneumonectomy with or without intensity modulated radiotherapy, and non-palliative RT)

c) Prior intraoperative or intracavitary chemotherapy for pleural mesothelioma.

d) Subjects with previous malignancies (except non-melanoma skin cancers, and in situ cancers such as the following: bladder, gastric, colon, cervical/dysplasia, melanoma, or breast) are excluded unless a complete remission was achieved at least 3 years prior to first

treatment and no additional therapy is required or anticipated to be required during the study period.

e) Other active malignancy requiring concurrent intervention or where concurrent intervention is anticipated while on study.

f) Subjects with an active, known or suspected autoimmune disease. 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.

g) Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of first treatment. Inhaled or topical steroids, and adrenal replacement steroid > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

h) Subjects with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity.

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

j) Subjects with serious or uncontrolled medical disorders

k) Treatment with botanical preparations (eg herbal supplements or traditional Chinese medicines) intended for general health support or to treat the disease under study within 2 weeks prior to randomization/treatment.

3. Physical and Laboratory Test Findings

a) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). Positive test for human immunodeficiency virus (HIV).
NOTE: Testing for HIV must be performed at sites where mandated locally (eg, Germany, South Africa).

b) Any positive test result for hepatitis B virus or hepatitis C virus indicating presence of virus, e.g. Hepatitis B surface antigen (HBsAg, Australia antigen) positive, or Hepatitis C antibody (anti-HCV) positive (except if HCV-RNA negative)

c) Inadequate hematologic, renal or hepatic function defined by any of the following screening laboratory values:

i) WBC < 2000/μL

ii) Neutrophils < 1500/μL

iii) Platelets < 100 x 10^3/μL

iv) Hemoglobin <9.0 g/dL

v) Serum creatinine >1.5 x ULN unless creatinine clearance ≥ 40 mL/min (measured or calculated using the Cockroft-Gault formula)

vi) AST/ALT >3.0 x ULN (> 5 x ULN if liver metastases)

vii)Total Bilirubin >1.5 x ULN (except subjects with Gilbert Syndrome who must have a total bilirubin level < 3.0 mg/dL)

4. Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to platinum-containing compounds or other study drug components

5. Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated. (Note: under certain specific circumstances a person who has been imprisoned may be included or permitted to continue as a subject. Strict conditions apply and Bristol-Myers Squibb approval is required).

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

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. Subjects not meeting the inclusion/exclusion criteria must not be enrolled into the study. There can be no exceptions to this rule.

3.3.3 Women of Childbearing Potential

Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) 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 > 40 mIU/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 judgement in checking serum FSH levels.

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

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal.

[redacted]

[redacted]

3.5 Discontinuation of Subjects following any Treatment with Study Drug

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

- Subject's request to stop study treatment
- Any clinical adverse event (AE), laboratory abnormality or concurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Disease progression (must be confirmed by BICR prior to discontinuation of treatment)
- 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
- Pregnancy*
- Additional protocol-specified reasons for discontinuation as per Section 4.5.5.
- Global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration' in the source data and in the case report form. Tumor assessments for subjects who discontinue study treatment without radiographic progression, should continue as per protocol until radiographic progression is determined.

*In the case of pregnancy, the investigator must immediately notify the Sponsor or designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). Please contact the Sponsor or designee within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the Sponsor or designee must occur, if local regulations allow.

All subjects who discontinue study drug should comply with protocol specified follow-up procedures as outlined in Section 5.1. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study drug 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 primary endpoint. 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 5.1 until death or the conclusion of the study.

BMS may request that survival data be collected on all treated/randomized subjects outside of the protocol defined window. At the time of this request, each subject will be contacted to determine

their survival status unless the subject has withdrawn consent for all contacts or is lost to follow-up.

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study drug 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 study drug 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 CA209743:

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
Nivolumab injection[a]	100 mg/vial (10 mg/mL)	IP	Open Label	10mL vial containing a clear to opalescent, colorless to pale yellow liquid; may contain particulates; 5 vials/carton	Store 2 to 8°C. Store in original package. Do not freeze. Protect from light.
Ipilimumab injection	200 mg/vial (5 mg/mL)	IP	Open Label	40mL vial containing a clear, colorless liquid; may contain particulates;4 vials/carton	Store 2 to 8°C. Store in original package. Do not freeze. Protect from light.
Cisplatin Concentrate for solution for infusion[b]	100mg/vial (1 mg/ml)	IP	Open Label	100mL vial containing a clear, colorless solution; 4 vials/carton	Do not store above 25°C. Do not refrigerate or freeze. Keep the vial in the outer carton.
Cisplatin Infusion (China)	Varies as per market product	IP	Open-label	As per market product	Store as indicated on market product.
Carboplatin Solution for IV Injection[b]	450 mg/vial (10 mg/mL)	IP	Open Label	45mL vial containing a sterile, colorless to slightly yellow aqueous solution; 4 vials/carton	Store at or below 25°C. Protect from light.
Carboplatin Injection (China)	Varies per market product	IP	Open-label	As per market product	Store as indicated on market product
Pemetrexed	500mg/vial	IP	Open Label	White to either light yellow or green-yellow lyophilised powder, 1 vial/carton	Store at 25°C. Excursions permitted (15-30°C)
Pemetrexed Disodium for Injection (China)	500 mg/vial	IP	Open label	As per market product	Store as indicated on market product

[a] May be labeled as either "BMS-936558-01" or "nivolumab".

[b] These products may be obtained by the investigational sites as local commercial product in certain countries if allowed by local regulations. In these cases, products may be a different pack size/potency than listed in the table. These products should be prepared/stored/administered in accordance with the package insert or summary of product characteristics (SmPC).

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. These include 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.

4.2 Non-investigational Product

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

Premedication used with Pemetrexed (Vitamin supplementation and dexamethasone) will not be supplied by Bristol-Myers Squibb.

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.

Investigational product documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

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

For nivolumab and ipilimumab, please refer to the current version of the Investigator Brochures and/or pharmacy reference sheets for complete storage, handling, dispensing, and infusion information.

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

4.4 Method of Assigning Subject Identification

After the subject's initial eligibility is established and informed consent has been obtained, the subject must be enrolled into the study by an interactive web response system (IWRS) to obtain the subject number. Every subject that signs the informed consent form must be assigned a subject number in IWRS. Specific instructions for using IWRS 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
- Archived tumor tissue submission date

Once enrolled in IWRS, subjects that have met all eligibility criteria will be ready to be randomized through IWRS. The following information is required for subject randomization:

- Subject number
- Date of birth
- Gender at birth
- Tumor histology: epithelioid vs sarcomatoid or mixed histology

Subjects will be randomized in a 1:1 ratio to one of two treatment arms.

Enrollment will stop once approximately 600 subjects have been randomized.

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

4.5 Selection and Timing of Dose for Each Subject

The dosing schedule is detailed below in Table 4.5-1.

All subjects will be monitored continuously for AEs while on study treatment. Treatment modifications (eg, dose delay, reduction, retreatment, or discontinuation) will be based on specific laboratory and adverse event criteria, as described in Sections 4.5.2, 4.5.3, 4.5.4, 4.5.5.

Table 4.5-1: Dosing Schedule (Arm A: 1 Cycle=6 weeks; Arm B: 1 Cycle=3 weeks)

	Week1 ± 3days	Week2	Week3 ± 3days	Week4	Week5 ± 3days	Week6
Arm A[a,b,c] Nivolumab 3 mg/kg q 2 wks + Ipilimumab 1 mg/kg q 6 wks	**Cycle 1 Day 1** Nivolumab +Ipilimumab		**Cycle 1 Day 15** Nivolumab		**Cycle 1 Day 29** Nivolumab	
Arm B[c,d,e] Pemetrexed 500mg/m^2 ± Cisplatin 75mg/m^2 (or Carboplatin AUC 5)	**Cycle 1 Day 1** Pemetrexed +Cisplatin (or Carboplatin)			**Cycle 2 Day 1** Pemetrexed +Cisplatin (or Carboplatin)		

[a] Both nivolumab and ipilimumab should be administered as 30 minute infusions. Nivolumab is to be administered first. The second infusion will be ipilimumab and will start at least 30 minutes after completion of the nivolumab infusion.

[b] Treatment continued until discontinuation due to toxicity, withdrawal of consent, maximum treatment duration of 2 years, or study closure. In the event of investigator assessed radiographic disease progression, treatment may be delayed until confirmation of progression by BICR.

[c] Pre-treatment oral folic acid 350 to 1000 µg daily should be given starting 1 week prior to the first dose. Intramuscular vitamin B12 1000 µg premedication is required approximately 1 week prior to cycle 1 day 1. On Arm B only, repeat intramuscular vitamin B12 1000 µg during treatment as per local policy.

[d] Recommendation is to administer dexamethasone 4 mg orally twice daily the day before, the day of, and the day after pemetrexed administration. Sites to follow local policy for corticosteroids administration.

[e] Treatment to continue for 6 cycles until disease progression or unacceptable toxicity. In the event of investigator assessed radiographic disease progression, treatment may be delayed until confirmation of progression by BICR.

4.5.1 Dosing

4.5.1.1 Nivolumab plus Ipilimumab

Subjects will receive treatment with nivolumab as a 30 minute infusion 3 mg/kg every 2 weeks and ipilimumab as a 30 minute infusion 1 mg/kg every 6 weeks, starting on Day 1, until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first. Subjects should begin study treatment within 3 calendar days of randomization.

Dosing calculations should be based on the body weight assessed at baseline. It is not necessary to re-calculate subsequent doses if the subject's weight is within 10% of the weight used to calculate the previous dose. All doses should be rounded up to the nearest milligram per institutional standard. Subjects may be dosed no less than 12 days from the previous dose during every 2 weeks nivolumab dose. There will be no dose modifications allowed. Subjects should be carefully monitored for infusion reactions. If an acute infusion reaction is noted, subjects should be managed according to Section 4.8.2

When study drugs (nivolumab and ipilimumab) are to be administered on the same day, nivolumab is to be administered first. Nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be the ipilimumab study drug and will start after the infusion line has been flushed, filters changed and subject has been observed to ensure no infusion reaction has occurred. The time in between infusions is expected to be approximately 30 minutes but may be more or less depending on the situation.

Nivolumab injection (10mg/mL) is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding in-line filter at the protocol-specified doses. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be infused undiluted (10mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP to 5% Dextrose Injection, USP, minimum protein concentrations can be found in the Investigator Brochure.

Instructions for dilution and infusion of nivolumab injection may be provided in the pharmacy binder, or pharmacy reference sheet. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

No incompatibilities have been observed between nivolumab injection and polyvinyl chloride (PVC), non-PVC/non-DEHP (di(2-ethylhexyl)phthalate) IV components, or glass bottles have been observed.

Ipilimumab injection (5 mg/mL) can be used for IV administration without dilution after transferring to a PVC (polyvinyl chloride), non-PVC/non-DEHP (di-[2-ethylhexyl]phthalate) or glass container, and is stable for 24 hours at 2ºC to 8ºC or room temperature/room light (RT/RL). The product may be infused using a volumetric pump at protocol specified dose through a PVC IV solution infusion set with an in-line, sterile, nonpyrogenic, low-protein-binding filter (pore size of 0.2 micrometer to 1.2 micrometer). The drug can be diluted with 0.9% normal saline or 5% Dextrose Injection to concentrations between 1 mg/mL and 4 mg/mL. Ipilimumab injection must not be administered as an IV push or bolus injection. Care must be taken to assure sterility of the

prepared solutions since the drug product does not contain any antimicrobial preservatives or bacteriostatic agents. At the end of the infusion, flush the line with a sufficient quantity of normal saline or 5% dextrose solution. For ipilimumab storage instructions, refer to ipilimumab IB and/or pharmacy reference sheets.

Separate infusion bags and filters should be used when administering nivolumab and ipilimumab on the same day.

Doses of nivolumab and/or ipilimumab may be interrupted, delayed, or discontinued depending on how well the subject tolerates the treatment. Dosing visits are not skipped, only delayed. For more details, see Section 4.5.2.1 for dose delays, Section 4.5.4 for resuming treatment, and 4.5.5.1 for treatment discontinuation.

Refer to the nivolumab and ipilimumab IBs and pharmacy manuals for specific infusion preparation recommendations.

4.5.1.2 Pemetrexed plus Cisplatin or Carboplatin

Subjects randomized to Arm B will receive treatment with pemetrexed at a dose of 500 mg/m² as a 10-minute IV infusion on Day 1 of a q 21 days cycle with cisplatin at a dose of 75 mg/m² or carboplatin Area Under the Curve (AUC) 5 as a IV infusion as per label, on Day 1 of every 21 days per cycle for 6 cycles.

Cisplatin or carboplatin in combination with pemetrexed will be administered according to label and/or local policy in terms of infusion schema (including but not limited to hydration protocols). The use of cisplatin is preferred, however, carboplatin may be used at the discretion of the investigator. Switching from cisplatin to carboplatin and vice versa are allowed, and the reason for that switch must be reported in the CRF. If switching is due to toxicity and either cisplatin or carboplatin is discontinued, the other study drug may be continued for the remainder of the cycles.

4.5.1.3 Pre-medications for use with Pemetrexed and Cisplatin:

- Oral corticosteroid should be given according to local standards or at a dose equivalent to dexamethasone 4 mg BID on the day prior to, the day of, and the day after the administration of pemetrexed. Oral folic acid 350 to 1000 μ g daily should be given starting 1 week prior to the first dose of pemetrexed, with at least 5 doses of folic acid administered in the 7 days prior to the first dose. Oral folic acid should be continued daily throughout the treatment with pemetrexed and for 21 days after the last dose of pemetrexed. Intramuscular (IM) injection of vitamin B12 1000 μ g should be given approximately one week prior to the first dose of pemetrexed with repeat administration during treatment as per local policy.
- Prior to pemetrexed and cisplatin/carboplatin infusion, antiemetic premedication will be administered according to local standards. Recommended antiemetic treatments are dexamethasone (dosing according to local standards; an equivalent dose of another corticosteroid may be substituted) and a 5-HT3 receptor antagonist (type per investigator discretion and local standards-of-care). Additional use of antiemetic pre-medications may be employed at the discretion of the Investigator.

4.5.2 Dose Delay Criteria

4.5.2.1 Dose Delay Criteria for Nivolumab plus Ipilimumab

In the case of investigator assessed radiographic progression of disease, dosing may be delayed until confirmation of progression by independent central review. If the independent central review report does not confirm disease progression, treatment must be continued.

Dose delay criteria apply to all drug-related AEs. Treatment delay up to 6 weeks for nivolumab and up to 12 weeks for ipilimumab from the last dose are allowable (any dose delays greater than these will require approval from the medical monitor).

Tumor assessments for all subjects should continue as per protocol even if dosing is delayed. Nivolumab and ipilimumab administration should be delayed for the following:

- Grade 2 non-skin, drug-related adverse event, except for fatigue
- Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities
- Grade 3 skin drug-related AE
- Grade 3 drug-related laboratory abnormality with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require a dose delay nor requires consultation with the medical monitor
  - Grade ≥ 3 AST, ALT, Total Bilirubin will require dose discontinuation
- Any AE, laboratory abnormality or inter-current illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Subjects receiving ipilimumab in combination with nivolumab that have drug-related toxicities that meet the criteria for dose delay, should have both drugs (ipilimumab and nivolumab) delayed until retreatment criteria are met.

Rescheduling:

- Nivolumab may be delayed until the next planned ipilimumab dose if the next ipilimumab dose is scheduled within the next 12 days. This will permit periodic ipilimumab dosing to be synchronized with nivolumab dosing.
- Ipilimumab should be dosed at the specified interval regardless of any delays in intervening nivolumab doses. However, in order to maintain periodic synchronized dosing of ipilimumab and nivolumab, the dosing days of nivolumab and ipilimumab may be adjusted within the permitted ±3 day window, as long as consecutive nivolumab doses are given at least 12 days apart. Ipilimumab may be delayed beyond the 3 day window if needed to synchronize with the next nivolumab dose.
- If an ipilimumab dose is delayed beyond 6 weeks from the prior ipilimumab dose, then subsequent Ipilimumab doses should be rescheduled to maintain the 6 week interval between consecutive Ipilimumab doses.
- A dose delay of ipilimumab which results in no ipilimumab dosing for > 12 weeks requires Ipilimumab discontinuation with following exception: Dosing delays to manage drug-related adverse events, such as prolonged steroid tapers, are allowed. Prior to re-initiating treatment

in a subject with a dosing delay lasting > 12 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.

4.5.2.2 Dose Delay Criteria for Pemetrexed and Cisplatin or Carboplatin

In the case of investigator assessed radiographic progression of disease, dosing may be delayed until confirmation of progression by independent central review. If the independent central review report does not confirm disease progression, treatment must be continued.

Pemetrexed and cisplatin or carboplatin should be both delayed for the following:

- Absolute neutrophil count (ANC) < 1500/µL or Presence of febrile neutropenia
- Platelets < 100,000/mm3
- Any Grade ≥ 2 non-skin, non-hematologic, drug-related adverse event, except for alopecia, fatigue or laboratory abnormalities
- Any Grade ≥ 3 skin drug-related AE
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions:
    - Grade 3 lymphopenia does not require a dose delay
    - If a subject has a baseline AST, ALT or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity.
    - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication. Investigators should consult local labeling for the chemotherapy drugs being administered to any given subject for additional guidance on dose delays.

In addition, subjects must discontinue cisplatin if the calculated creatinine clearance decreases to < 50 mL/min (based on the Cockroft Gault formula). Pemetrexed may be continued, and the platinum agent may, at the investigator's discretion, be switched to carboplatin for the remainder of the platinum doublet cycles when the subject meets the criteria to resume dosing as specified in Section 4.5.4.3.

If any non-hematologic adverse event meeting the dose delay criteria above is felt to be related to only one particular agent in the platinum doublet chemotherapy regimen, then that agent alone may be omitted for that cycle while the other agent is given. In order to maintain synchronized dosing of the regimen, the omitted agent should be resumed with the next scheduled cycle once the AE has improved and retreatment criteria are met.

Subsequent dose reductions may be required as per Section 4.5.3.2. Subjects with hematologic toxicity may receive growth factors (including G-CSF and erythropoietin) at the discretion of the investigator.

If both drugs in the platinum doublet chemotherapy regimen are delayed, then the subject should be re-evaluated weekly or more frequently if clinically indicated until re-treatment criteria are met (as per Section 4.5.4.3).

4.5.3 Dose Reductions

4.5.3.1 Nivolumab or Ipilimumab

There will be no dose reductions for nivolumab or ipilimumab.

4.5.3.2 Pemetrexed and Cisplatin or Carboplatin

This section includes information on dose modifications for pemetrexed, cisplatin and carboplatin. A maximum of 2 dose reductions per study drug are permitted; if additional reductions are required, that particular study drug must be discontinued. Once a dose has been decreased, it should remain reduced for all subsequent dosing unless dose is further reduced. No dose escalations will be allowed. If one of the study drugs is delayed due to drug related toxicities during a treatment cycle, the other study drugs in the regimen may be administered at the discretion of the investigator; when dosing is resumed, dose reduction should only be applied to the study drug that was withheld.

It is recommended that all participants who receive cisplatin should have audiometric testing performed prior to initiation of therapy and prior to subsequent doses of cisplatin, as per local or institutional standards of care. Recommendations for dose modifications for pemetrexed cisplatin and carboplatin should be considered with local institutional standards. The dose levels for Pemetrexed, Cisplatin and carboplatin are listed in Table 4.5.3.2-1:

Table 4.5.3.2-1: Dose Levels for Pemetrexed, Cisplatin, and Carboplatin

	Pemetrexed	Cisplatin	Carboplatin
Starting Dose	500 mg/m²	75 mg/m²	AUC 5.0
Dose Level -1	375 mg/m²	56 mg/m²	AUC 4.0
Dose Level -2	250 mg/m²	38 mg/m²	AUC 3.0
Dose Level -3	Stop drug	Stop drug	Stop drug

- ***Hematologic Toxicity***

Dose modification guidelines for hematologic toxicities (according to CTCAE version 4) are summarized in Table 4.5.3.2-2. Dose adjustments for hematologic toxicity at the start of a subsequent cycle should be based on nadir hematologic counts from the previous cycle of therapy; treatment may be delayed to allow the hematologic toxicities to return to Grade 1. After the first cycle, growth factors are permissible to allow for hematological recovery. Please use local standards of care in the use of these supportive measures.

Additionally, the use of prophylactic dose antibiotics is to be used according to local standards of care. Please note any antibiotic or growth factor use on the eCRF.

Table 4.5.3.2-2: Dose Modifications for Hematologic Toxicities			
Toxicity	**Pemetrexed**	**Cisplatin**	**Carboplatin**
Neutrophil count Decreased Grade 4 (< 500/mm3 or <0.5 x 10^9/L)	Reduce one dose level	Reduce one dose level	Reduce one dose level
Anemia Grade 2 (< 10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80 g/L)	Reduce one dose level	No change	No change
Anemia Grade 3 (< 8.0 g/dL; < 4.9 mmol/L; < 80 g/L)	Reduce one dose level	Reduce one dose level	Reduce one dose level
Anemia Grade 4 (Life threatening consequences)	Hold drug	Hold drug	Hold drug
Platelet count decreased Grade 3 (< 50,000 - 25,000/mm3; < 50.0 - 25.0 x 10^9/L)	No change	No change	No change
Platelet count decreased Grade 4 (< 25,000/mm3; < 25.0 x 10^9/L)	Reduce one dose level	Reduce one dose level	Reduce one dose level

- ***Non-hematologic Toxicity***

Dose modification guidelines for non-hematologic toxicities (according to CTCAE version 4) are summarized in Table 4.5.3.2-3. Treatment may be delayed to allow the non-hematologic toxicities to return to Grade 2 or back to baseline (excluding alopecia and skin and nail changes).

Table 4.5.3.2-3: Dose Modifications for Non-hematologic Toxicity[a]

Toxicity	Pemetrexed	Cisplatin	Carboplatin
Febrile Neutropenia Grade ≥ 3	Reduce one dose level	Reduce one dose level	Reduce one dose level
Diarrhea Grade ≥ 3	Reduce one dose level	No change	No change
Allergic Reaction Grade ≥ 3	Reduce one dose level	Reduce one dose level	Reduce one dose level
Paresthesia Grade 2	No change	Reduce one dose level	Reduce one dose level
Paresthesia Grade ≥ 3	Reduce one dose level	Reduce two dose levels	Reduce two dose levels

[a] If considered in the best interest of the subject, and consistent with local practice, investigators may decide to use supportive measures/treatment, and/or secondary prophylaxis instead of dose reductions for the next cycle. Also, if toxicity can clearly be attributed to one of the drugs, the investigator may choose to only dose reduce one of the cytotoxics.

Cisplatin induces nephrotoxicity, which is cumulative, it is therefore contra-indicated in subjects with renal impairment. Dose adjustment for cisplatin after recovery from renal toxicity is allowed as per Section 4.5.4.3, and carboplatin should also be considered as per local institutional standards.

4.5.4 Criteria to Resume Dosing

4.5.4.1 Criteria to Resume Nivolumab Dosing

Subjects may resume treatment with study drug 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
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- For subjects with Grade 2 AST/ALT, or total bilirubin elevations, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 4.5.5.1) 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 a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by BMS Medical Monitor.

- Subjects who received systemic corticosteroids for management of any drug-related toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone ≤ 10 mg/day.
- Subjects with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor.
- Dose delay of nivolumab which results in treatment delay of > 6 weeks requires treatment discontinuation, with exceptions as noted in Section 4.5.5.1.

4.5.4.2 Criteria to Resume Ipilimumab Dosing

Subjects may resume treatment with nivolumab and ipilimumab when drug-related AE(s) resolve(s) to Grade 1 or baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-Grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT or total bilirubin.
- Subjects with combined Grade 2 AST/ALT and total bilirubin values meeting discontinuation parameters (Section 4.5.5.2) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed.
- Subjects who received systemic corticosteroids for management of any drug-related toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone ≤ 10 mg/day.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor.
- Dose delay of ipilimumab which results in no ipilimumab dosing for > 12 weeks requires ipilimumab discontinuation, with exceptions as noted in Section 4.5.5.2.
- Ipilimumab may not be resumed sooner than 6 weeks (± 3 days) after the prior ipilimumab dose.
- In general, subjects who meet criteria to resume ipilimumab will also have met criteria to resume nivolumab, so it should be feasible to synchronize dosing of both drugs when resuming ipilimumab. In order to facilitate this, the dosing days of nivolumab and ipilimumab may be adjusted within the permitted ± 3 day window, as long as consecutive nivolumab doses are given at least 12 days apart.

4.5.4.3 Criteria to Resume Dosing for Pemetrexed and Cisplatin or Carboplatin

- Subjects may resume treatment with platinum doublet chemotherapy when the ANC returns to ≥ 1500/µl, the platelet count returns to ≥ 100,000/mm3, and all other drug-related toxicities have returned to baseline or Grade ≤ 1 (or Grade ≤ 2 for alopecia and fatigue).

- If a subject fails to meet criteria for re-treatment, then re-treatment should be delayed, and the subject should be re-evaluated weekly or more frequently as clinically indicated.
- Any subject who fails to recover from toxicity attributable to platinum doublet chemotherapy to baseline or Grade ≤ 1 (except Grade 2 alopecia and fatigue) within 6 weeks from the last dose given should discontinue the drug(s) that caused the delay.

When resuming platinum doublet chemotherapy treatment, please follow the dose reduction recommendations in Section 4.5.3.2.

4.5.5 Treatment Discontinuation Criteria

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

4.5.5.1 Nivolumab Dose Discontinuation

Nivolumab treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis, 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 drug-related bronchospasm, hypersensitivity reaction, or infusion reaction, regardless of duration;
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for drug related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reactions, infusion reactions, endocrinopathies, and laboratory abnormalities:
- Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation.
- Any 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 > 2x 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 ratio 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 adverse event or laboratory abnormality (including but not limited to creatinine, AST, ALT, or Total Bilirubin), except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase
  - 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
  - Grade 4 drug-related endocrinopathy adverse events, such as, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor. Grade 4 adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
- Any event that leads to delay in dosing lasting > 6 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks from the previous dose, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.
  - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor. Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.

Note: If nivolumab is discontinued for any reason, ipilimumab may not be continued alone.

4.5.5.2 Ipilimumab Dose Discontinuation

Ipilimumab should be permanently discontinued if any of the following criteria are met:

- 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 2 weeks OR requires systemic treatment;
- Any Grade ≥ 3 bronchospasm or other hypersensitivity reaction;
- Any other Grade 3 non-skin, drug-related adverse with the following exceptions for laboratory abnormalities, Grade 3 nausea and vomiting, Grade 3 neutropenia and thrombocytopenia, and symptomatic endocrinopathies which resolved (with or without hormone substitution);

- Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
  - AST or ALT > 8 x ULN
  - Total bilirubin > 5 x ULN
  - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events, which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia
  - Grade ≥ 3 amylase or lipase abnormalities not associated with symptoms or clinical manifestations of pancreatitis
- Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
- Any treatment delay resulting in no ipilimumab dosing for > 12 weeks with the following exceptions: Dosing delays to manage drug-related adverse events, such as prolonged steroid tapers, are allowed. Prior to re-initiating treatment in a subject with a dosing delay lasting > 12 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.
- Dosing delays resulting in no ipilimumab dosing for > 12 weeks that occur for non-drug related reasons may be allowed if approved by the BMS medical monitor. Prior to re-initiating treatment in a subject with a dosing delay lasting > 12 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued ipilimumab dosing

The assessment for discontinuation of ipilimumab should be made separately from the assessment made for discontinuation of nivolumab. Although there is overlap among the discontinuation criteria, if discontinuation criteria are met for ipilimumab but not for nivolumab, treatment with nivolumab may continue if ipilimumab is discontinued.

If a subject meets criteria for discontinuation and investigator is unable to determine whether the event is related to both or one study drug, the subject should discontinue both nivolumab and ipilimumab and be taken off the treatment phase of the study.

4.5.5.3 Pemetrexed and Cisplatin or Carboplatin Dose Discontinuation

Except where specified below, both chemotherapy drugs in the platinum doublet chemotherapy regimen should be discontinued for any of the following:

- Any Grade ≥ 3 peripheral neuropathy
- Grade ≥ 3 drug-related thrombocytopenia associated with clinically significant bleeding
- Any drug-related liver function test (LFT) abnormality that meets the following criteria requires discontinuation:

  - AST or ALT > 5-10x ULN for > 2 weeks
  - AST or ALT > 10x ULN
  - Total bilirubin > 5 x ULN
  - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Any cisplatin-related decrease in creatinine clearance to < 50 mL/min (using the Cockroft Gault formula) requires discontinuation of cisplatin
- Any drug-related adverse event which recurs after two prior dose reductions for the same drug-related adverse event (as specified in Sections 4.5.3.2) requires discontinuation of the drug(s) which was/were previously dose reduced.
- Any Grade ≥ 3 drug-related hypersensitivity reaction or infusion reaction requires discontinuation of the drug(s) felt to be causing the reaction. The drug not felt to be related to the hypersensitivity reaction or infusion reaction may be continued.
- Any Grade 4 drug-related adverse event which the investigator deems is inappropriate to be managed by dose reduction(s) requires discontinuation of the drug(s) felt to be causing the event. The drug not felt to be related to the event may be continued.
- Any event that leads to delay in dosing of any study drug(s) for > 6 weeks from the previous dose requires discontinuation of that drug(s) with the following exception:
  - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor. Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks, the BMS medical monitor must be consulted. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued platinum doublet chemotherapy dosing. Investigators should consult local labeling for the chemotherapy drugs being administered to any given subject for additional guidance on dose discontinuation.
- Subjects receiving pemetrexed/cisplatin who discontinue cisplatin alone may, at the investigator's discretion, be switched to pemetrexed/carboplatin for the remainder of the platinum doublet cycles, when the subject meets retreatment criteria, as specified in Section 4.5.4.3.

4.6 Treatment Beyond Disease Progression (Arm A only)

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD.

Subjects will be permitted to continue on nivolumab plus ipilimumab for treatment beyond initial adapted m-RECIST for mesothelioma and/or RECIST 1.1 defined PD as long as they meet the following criteria:

  - Investigator-assessed clinical benefit.
  - Tolerance of study drug
  - Stable performance status

- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
- **Subject provides written informed consent prior to receiving additional nivolumab and ipilimumab treatment. All other elements of the main consent including description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply.**

The decision to continue treatment beyond initial investigator-assessed and independent central review confirmed progression must be approved by the BMS Medical Monitor and documented in the study records. A follow-up scan should be performed within six (6) weeks ± 7 days of original PD to determine whether there has been a decrease in the tumor size, or continued progression of disease.

If the investigator feels that the subject continues to achieve clinical benefit by continuing treatment, the subject should remain on the trial and continue to receive monitoring according to the Time and Events Schedule in Section 5.1.

For the subjects who continue nivolumab and ipilimumab study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden with a minimum 5 mm absolute increase from time of initial PD. This includes an increase in the sum of diameters of all target lesions and/ or the diameters of new measurable lesions compared to the time of initial PD. Nivolumab/ ipilimumab treatment should be discontinued permanently upon documentation of further progression.

New lesions are considered measureable 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 least15 mm). Any new lesion considered non-measureable at the time of initial progression may subsequently become measureable and therefore included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of new lesions which become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

4.7 Blinding/Unblinding

An open-label (rather than blinded) study design was selected because the management of similar AEs will differ between treatment arms, given the different mechanisms of action of different treatment arms. If this trial is blinded, the management of AEs would potentially be delayed or detrimental to the subject.

4.8 Treatment Compliance

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

[redacted]

4.8.2 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 an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE (Version 4) 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 acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional nivolumab or ipilimumab administrations.

For Grade 2 symptoms: (moderate reaction required 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 nivolumab or ipilimumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid and/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 nivolumab or ipilimumab 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 study drug infused must be recorded on the electronic case report form (eCRF).

- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before nivolumab or ipilimumab infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

For Grade 3 or 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 nivolumab or ipilimumab. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 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. Nivolumab or ipilimumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms.

In 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).

4.9 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.

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 (eg, cytotoxic or biologics).

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 additional guidance on IP records and documentation.

4.10 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 (CA209743)

Procedure	Screening Visit	Notes
Eligibility Assessments[a]		
Informed Consent	X	Original IC in screening for protocol participation; Study allows for re-enrollment of a subject that has discontinued the study as a pre-treatment failure. If re-enrolled, the subject must be re-consented and assigned a new subject number from IWRS.
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening and confirmed prior to first dose.
Medical History	X	
Tumor Tissue Sample Collection	X	Tumor sample for PD-L1 testing is mandatory, to be shipped to Central Laboratory up to 42 days prior to randomization. A fresh or archived pre-treatment tumor biopsy specimen within 6 months of randomization is required for full eligibility of a subject. A minimum of 1 formalin-fixed paraffin embedded (FFPE) tumor tissue block (preferred) OR a minimum of 10 FFPE unstained sections are required. Subjects can initiate therapy before the result of PD-L1 IHC testing.
Screening/Baseline Tumor Assessment	X	CT scan of chest and upper abdomen (upper abdomen includes imaging down to the iliac crests), and all other known sites of disease within 28 days prior to first dose. Tumor assessments follow modified m-RECIST for malignant pleural mesothelioma and RECIST 1.1 criteria for metastatic lesions. Up to 6 pleural measurements are required for the study and each pleural measurement must be $\geq$ 10 mm in length.
Prior Medications	X	Any prior medications subjects received to treat cancer.
Safety Assessments		
Physical Examination/Physical Measurements/ECOG Performance Status	X	Height, weight, BSA (screening only), signs and symptoms within 14 days prior to first dose

Table 5.1-1: Screening Procedural Outline (CA209743)

Procedure	Screening Visit	Notes
Vital Signs	X	Obtain vital signs (BP, HR, RR and temperature) at the screening visit and within 72 hours prior to first dose. Vital sign measurements are to be performed in same position as the first measurement and for all subsequent visits.
Serious Adverse Events Assessment	X	From time of informed consent
[redacted]	[redacted]	[redacted]
ECG	X	Within 14 days prior to first dose. ECG QTc calculation as per SOC.
Laboratory Tests	X	CBC w/differential, Chemistry panel including: Albumin , LDH, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, phosphate, glucose, amylase, lipase, TSH, Free T4, Free T3, Hepatitis B surface antigen (HBV sAg), hepatitis C antibody (HCV Ab) or Hepatitis C RNA (HCV RNA), and HIV (where locally mandated, [eg, required for sites in Germany and South Africa]). Within 14 days prior to first treatment. Subjects who test positive for hepatitis C but have undetectable HCV RNA are allowed to enroll
Pregnancy Test (WOCBP only)	X	Serum or urine within 24 hours of first dose
Tumor Tissue sample:	X	A fresh or archived tumor tissue sample is mandatory, to be shipped to Central Laboratory prior to randomization
Study Drug		
Enrollment in IWRS	X	Subjects will be randomized upon all screening assessment completion. Randomization assignment must occur at least 24 hours prior to first dosing day to allow for pre-medication dexamethasone regimen for Arm B.

[a] All screening assessments must be completed and subject should be treated within 28 days, except ECOG, physical assessments, signs and symptoms, concomitant medication, ECG and laboratory tests should be done within 14 days prior to first treatment, vital signs within 72 hours, pregnancy test must be within 24 hours prior to first dose, and ICF must be signed, screening CT, and tumor sample must be shipped within 42 days before randomization.

Table 5.1-2: On Treatment Procedural Outline (CA209743)

Procedure	During Treatment Visit [a,b,c]	Notes
Safety Assessments		
Physical Examination/Physical Measurements (including performance status)	X	Weight and ECOG status. The dosing calculations for nivolumab and ipilimumab should be based on the body weight assessed at baseline. It is not necessary to re-calculate subsequent doses if the participant weight is within 10% of the weight used to calculate the previous dose. All doses should be rounded up or to the nearest milligram per institutional standard. Pemetrexed, Cisplatin and Carboplatin dose calculation should be as per local policy. Physical exam must be performed on day of treatment
Vital Signs	X	BP, HR, and temperature must be performed on day of treatment and prior to dosing for both treatment Arms. Vital sign measurements are to be performed in same position as the first measurement and for all subsequent visits.
Adverse Events Assessment	X	
Laboratory Tests	X	On-study local laboratory assessments should be done within 3 days prior to each dose. CBC w/differential, (Albumin if clinically indicated), LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, phosphate, glucose, amylase, lipase, TSH with reflexive Free T4, and Free T3. (Thyroid Function Testing to be evaluated every 6 weeks) Arm B: amylase and lipase testing are not required.
Pregnancy Test (WOCBP only)	X	Serum or urine within 24 hours prior to first dose and then every 4 weeks (+ - 1 week) regardless of dosing schedule
Efficacy Assessments		
Tumor Assessments	X	Response will be assessed at 6 weeks (± 7 days) from first dose date, then every 6 weeks (±7 days) for the first 12 months (until week 48) and every 12 weeks (± 7 days) thereafter, until BICR confirmed disease progression is documented.
Outcomes Research Assessments		
[redacted]	[redacted]	[redacted]

Table 5.1-2: On Treatment Procedural Outline (CA209743)

Procedure	During Treatment Visit [a,b,c]	Notes
[redacted]		[redacted]
Healthcare Utilization	X	To be completed by the site in CRF.
[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]
Clinical Drug Supplies		
IWRS Drug Vial Assignment	X	
Dispense Study Drug	X	Within 3 days from randomization, the subject should receive the first dose of study medication.
Premedication	X	See Section 3.1

[a] Cycle length: Arm A 1 Cycle = 6 weeks; Arm B 1 Cycle = 3 weeks.

[b] Arm A: Visits occur every 2 weeks

[c] Arm B: Visits occur every 3 weeks

Table 5.1-3: Follow up period (CA209743): Both treatment arms

Procedure	Follow up Visit 1 and 2[a]	Survival follow up[b]	Notes
Safety Assessments			
Targeted Physical Examination	X		To assess for potential late emergent study drug related issues
Vital Signs	X		
Adverse Events Assessment	X	X	In survival period only to include toxicities from study therapy
Laboratory Tests	X		CBC w/ differential, LFTs, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH (+ reflex Free T4 and Free T3). All tests are to be done at FU1, and repeated at FU2, if study related toxicity persists. Arm B: amylase and lipase testing are not required.
[redacted]			[redacted]
[redacted]	[redacted]		[redacted]
Efficacy Assessments			
Tumor Assessments	X	X	Only for subjects without progression. Tumor assessments should occur every 6 weeks (± 7 days) from first dose date, then every 6 weeks ± 7 days) for the first 12 months (until week 48) and every 12 weeks (± 7 days) thereafter, until BICR confirmed disease progression is documented.
[redacted]			
[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Table 5.1-3: Follow up period (CA209743): Both treatment arms

Procedure	Follow up Visit 1 and 2[a]	Survival follow up[b]	Notes
Subject Status			
Survival Status	X	X	Every 3 months after FU 2; may be accomplished by visit, phone contact or email, to include assessment of subsequent anti-cancer therapy

[a] Follow-up visit 1 (FU1) = 30 days from the last dose ± 7 days or coincides with the date of discontinuation (± 7 days) if date of discontinuation is greater than 35 days after last dose, Follow-up visit 2 (FU2) = 90 days (± 7 days) from follow-up visit 1

[b] Every 3 Months (± 7 days) from FU2

NOTE: Arm B: After completion of Follow up Visit 1 and 2, subjects enter survival follow up and should only complete assessments for EQ-5D.

5.1.1 Retesting DuringScreening or Lead-in Period

Retesting of laboratory parameters and/or other assessments within any single Screening or Lead-in 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

- NCI CTCAE version 4
- nivolumab Investigator Brochure
- ipilimumab Investigator Brochure
- Pharmacy Binder
- Laboratory manuals for collection and handling of blood (including PK, biomarker and immunogenicity) and tissue specimens
- Site manual for operation of Interactive Voice Response System (IWRS), including enrollment worksheets
- Manual for entry of local laboratory data
- Pregnancy Surveillance Forms
- m-RECIST for malignant pleural mesothelioma pocket guide
- Study Imaging Manual

5.3 Safety Assessments

At screening, a medical history will be obtained to capture relevant underlying conditions. The screening examinations should include weight, height, ECOG Performance Status, blood pressure (BP), heart rate (HR), and temperature. Screening assessments should be performed within 28 days prior to first dose. Baseline signs and symptoms are those that are assessed within 14 days prior to first dose. Concomitant medications will be collected from within 14 days prior to the first dose through the study treatment period (see Section 5.1)

Screening local laboratory assessments should be done within 14 days prior to first dose and are to include: CBC with differential, Chemistry panel including LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Na, K, Cl, phosphate, LDH, glucose, and thyroid panel including TSH, free T3, and free T4.

The following baseline local laboratory assessments should be done within 14 days prior to first treatment: Hepatitis B and C testing (HBV sAg and HCV Ab or HCV RNA) and HIV testing (where locally mandated, [eg, required for sites in Germany and South Africa]).

.

Screening pregnancy tests for WOCBP must be performed within 24 hours prior to the initial administration of study drug.

While on-study the following local laboratory assessments are to be done within 3 days prior to each dose: CBC with differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, albumin (if clinically indicated), Ca, Mg, Na, K, Cl, phosphate, LDH, glucose, amylase, and lipase. Thyroid function testing is to be done every 6 weeks regardless of treatment arm.

Subjects will be evaluated for safety if they have received any study drug. Toxicity assessments will be continuous during the treatment phase as well as during the first two safety follow-up visits. Once subjects reach the survival follow-up phase, either in-person visits or documented telephone calls to assess the subject's status are acceptable.

Adverse events and laboratory values will be graded according to the NCI-CTCAE version 4.

The start and stop time of the study therapy infusions and any interruptions or infusion rate reductions should be documented.

Physical examinations are to be performed as clinically indicated. If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate non-serious or serious adverse event page.

Additional measures, including non-study required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug induced liver enzyme evaluations) will be monitored during the follow-up phase via on site/local labs until all study drug related toxicities resolve, return to baseline, or are deemed irreversible.

If a subject shows pulmonary-related signs (hypoxia, fever) or symptoms (eg, dyspnea, cough, fever) consistent with possible pulmonary adverse events, the subject should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm in the BMS-936558 (nivolumab) Investigator Brochure.

Some of the assessments referred to in this section may not be captured as data in the eCRFs. 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.

5.4 Imaging Assessment for the Study

Images will be submitted to an imaging third-party radiology vendor for central review. Sites will be trained prior to screening the first study subject. Image acquisition guidelines and submission process will be outlined in the study Imaging Manual provided by the radiology vendor. Tumor assessments should be submitted to the third-party radiology vendor as they are performed on an ongoing basis.

Screening assessments are to be performed within 28 days prior to first dose. All known sites of disease should be assessed at baseline. Recognizing that not all cases of advanced unresectable

malignant pleural mesothelioma can be assessed with 6 pleural measurements, the m-RECIST suggested guidance has been adapted in this study to allow for the assessment of up to 6 measurements rather than a fixed number. Measurements will be in up to 2 positions at 3 separate levels on transverse cuts of CT scan (cuts must be at least 10 mm apart). Each single tumor measurement must be at least 10 mm in length to qualify as measureable disease and contribute to the sum that defines the pleural uni-dimensional measurement. The maximum number of pleural lesions, up to 6, that qualify as measureable disease must be used. Known metastatic MPM non-pleural lesions (including nodal or subcutaneous lesions) meeting RECIST 1.1 criteria, will also be considered measurable disease.

Radiographic tumor response will be assessed at 6 weeks(± 7 days) from first dose date, then every 6 weeks (± 7 days) for the first 12 months (until week 48) and every 12 weeks (± 7 days) thereafter, until disease progression is documented.

Radiology assessments must be kept to schedule irrespective of any delays in a treatment cycle. If the schedule cannot be kept all attempts must be made to undertake the required imaging as soon as possible then subject must be put back on original imaging schedule.

Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible. Change in tumor measurements and tumor response will be assessed by the Investigator using the adapted m-RECIST and/or RECIST 1.1 criteria (See Appendix 4).

In addition, subjects receiving nivolumab and ipilimumab treatment beyond progression must continue tumor assessments until such treatment has been discontinued. See Section 4.6.

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.

5.5 Efficacy Assessments

The primary endpoint is overall survival (OS) in all randomized subjects. See Section 8.3.1for the definitions of OS. Every effort will be made to collect survival 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 survival 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.

The secondary efficacy endpoints of the study are overall response rate (ORR), disease control rate (DCR), and progression free survival (PFS), based on BICR assessment in all randomized subjects. See Section 8.3.2 for the definitions of ORR, DCR, and PFS. All randomized subjects will be monitored by radiographic assessment on an every-6-week schedule (± 7 days) for the first 12 months (until week 48) and every 12 weeks (± 7 days) thereafter [beginning from the first on-study assessment on week 6 (± 7 days)], to determine changes in tumor size. Adapted m-RECIST and RECIST 1.1 criteria will be used for the assessment.

[redacted]

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 study treatment 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 study treatment, whether or not considered related to the study treatment.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term
Events NOT Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

The causal relationship to 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 study drug administration and the AE.
- Not related: There is not a reasonable causal relationship between study drug administration and the AE.

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

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

Sponsor or designee 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 6.4 for the definition of potential DILI.)

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the 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 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 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 the last dose of study drug. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy). For subjects randomized/assigned to treatment and never treated with study drug, SAEs should be collected for 30days from the date of randomization/treatment assignment.

The investigator must report any SAE that occurs after these time periods and that is believed to be related to 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 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 study drug, and pregnancies must be reported to Sponsor 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 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 SUSAR (Suspected, Unexpected Serious Adverse Reaction) 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 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 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)should be collected continuously during the treatment period and for a minimum of 100 days following discontinuation of study treatment.

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 subject's case report form.

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

6.3 Pregnancy

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

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). Please call the Sponsor or designee within 24 hours of awareness of the pregnancy.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject.

The investigator must immediately notify the Sponsor or designee of this event and complete and forward a Pregnancy Surveillance Form to Sponsor 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.

6.4 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.

6.5 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.

6.5.1 Adverse Events of Interest

Definition of immune-mediated adverse events (IMAEs)

Immune-mediated AEs are specific events (that include pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, and endocrine (adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis) for which subjects received immunosuppressive medication for treatment of the event, with the exception of endocrine events (hypothyroidism/thyroiditis, hyperthyroidism, hypophysitis, diabetes mellitus, adrenal insufficiency), which are included regardless of treatment since these events are often managed without immunosuppression.

IMAEs include events, regardless of causality, occurring within 100 days of the last dose. This list is subject to change based on Health Authority feedback or change of MedDRA version. The final list used will be described in the CSR.

Table 6.5.1-1 below provides a summary of the IMAEs category and their respective PTs. This list is subject to change based on Health Authority feedback or change of MedDRA version. The final list used will be described in the CSR.

Table 6.5.1-1: Preferred Terms Included in Analysis of IMAEs to Support Warnings and Precautions

IMAE Category	PTs included under IMAE Category
Pneumonitis	Pneumonitis, Interstitial lung disease
Diarrhea/Colitis	Diarrhea, Colitis, Enterocolitis
Hepatotoxicity	Hepatotoxicity, Hepatitis, Hepatitis acute, Autoimmune hepatitis, AST increased, ALT increased, Bilirubin increased, ALP increased
Adrenal insufficiency	Adrenal insufficiency

Table 6.5.1-1: Preferred Terms Included in Analysis of IMAEs to Support Warnings and Precautions	
IMAE Category	**PTs included under IMAE Category**
Hypothyroidism/Thyroiditis	Hypothyroidism, Thyroiditis, Thyroiditis acute (collapsed with thyroiditis for frequency), Autoimmune thyroiditis (collapsed with thyroiditis for frequency)
Hyperthyroidism	Hyperthyroidism
Hypophysitis	Hypophysitis
Diabetes mellitus	Diabetes mellitus, Diabetic ketoacidosis
Nephritis and renal dysfunction	Nephritis, Nephritis allergic, Tubulointerstitial nephritis, Acute renal failure, Renal failure, Increased creatinine
Rash	Rash, Rash maculopapular

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, CA209743. 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. The DMC will act in an advisory capacity to BMS and will monitor subject safety data for the study.

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.

Blinded Independent Central Review (BICR)

A BICR will be employed for interpretation of radiographic progression events. At the time of investigator-assessed initial radiographic progression per adapted Modified RECIST and/or RECIST 1.1 criteria in any given subject, the site must request the independent central review from the third party radiology vendor for confirmation of progression.

Tumor assessments for each subject should be submitted to the radiology vendor as they are performed on an ongoing basis. The blinded, independent radiologists will review all available tumor assessments for that given subject and determine if adapted m-RECIST and/or RECIST 1.1 criteria for progression have been met. The independent assessment of whether or not the given subject met criteria for progression will be provided to the site. Subjects whose disease progression is not confirmed centrally will be required to continue treatment and tumor assessments according to the protocol-specified schedule. Subsequent tumor assessments must be submitted to the third

party radiology vendor for subsequent review and may be discontinued when the investigator and independent radiologists both assess the subject to have met criteria for progression.

The BICR will also review tumor images in all randomized subjects to determine adapted m-RECIST and/or RECIST 1.1 best overall response for the analyses of ORR.

At time of analysis of ORR, tumor assessments will use BICR in all randomized subjects to determine progression and response for the analyses of PFS and ORR. Details of the BICR responsibilities and procedures will be specified in the BICR charter.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

The study accounts for the primary endpoint of OS. Overall two-sided alpha (type one error rate) is set at 0.05. Approximately 600 patients were to be randomized with 1:1 ratio to two treatment arms, with 606 patients actually randomized. 473 OS events will be needed for the final analysis. The sample size is calculated to compare OS between nivolumab combined with ipilimumab (Arm A) and pemetrexed plus cisplatin or carboplatin regimen (Arm B). One formal interim analysis is planned for OS at 403 OS events. Table 8.1-1 summarizes the key parameters of trial design.

Overall survival: The key design parameters are shown in Table 8.1-1, where OS endpoint will utilize a group sequential design (GSD) with one interim analysis at 403 OS events and final analysis at 473 OS events. Stopping boundaries of GSD at the interim and final OS analyses will be derived based on the exact number of deaths using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. Given accrual rate of 34 patients per month, it is estimated that it will take approximately 38/56 months to observe the required number of events for the interim/final OS analysis.

An exponential distribution is assumed for the OS time of control Arm B with a median OS time of 16 months and hazard rate of 0.043. To capture some observed features on the survival curves of immuno-therapies, a piecewise exponential models is assumed for the survival time on nivolumab plus ipilimumab arm. In particular, a piecewise exponential with hazard rates of 0.043, 0.033, and 0.0001 in the following post first dose time windows: first 6 months, 6 months to 34 months, and after 34 months, will provide a delay of treatment effect in the first 6 months, an exponential distribution of OS from 6 months to 34 months, and a long term survival rate plateau starting approximately at 34 months. Simulation evaluation of trial design shows that the above piecewise exponential distribution will produce a 90% power in log-rank test. The numerical value of type one error rate in simulation is 5%.

If the same simple assumption of exponential distributions is assumed for OS times on Arm A, the study design has approximately 90% power to detect a hazard ratio of 0.72 (Arm A vs Arm B). The above sample size calculation was based on a simulation model incorporating aspects of immuno-oncology therapies, such as delayed separation and long term benefit using EAST 6.

Table 8.1-1: Summary of Key Design Parameters

Primary Endpoints	OS
Targeted Power	90%
Alpha	0.05 2-sided (0.03 at IA; 0.041 at FA)
Expected number of events for IA (percentage of target event)	403 (85%)
Target number of events	473
Duration (monthly accrual rate = 34 patients)	56 months

8.2 Populations for Analyses

- 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 arm in the study. This is the primary dataset for analyses of demography, protocol deviations, baseline characteristics, and efficacy.
- All treated subjects: all randomized subjects who received at least one dose of any study medication. This is the primary dataset for drug exposure and safety analysis.

[redacted]

8.3 Endpoints

8.3.1 Primary Endpoint

The primary endpoint for the study is OS. 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 study drug and every 3 months via in-person or phone contact after subjects discontinue the study drug.

8.3.2 Secondary Endpoint(s)

The secondary objectives will be measured by ORR, DCR, and PFS as assessed by BICR. ORR is defined as the proportion of all randomized subjects whose best overall response (BOR) from baseline is either a CR or PR per adapted m-RECIST and/or RECIST 1.1 criteria as assessed by BICR. DCR is defined as the proportion of all randomized subjects whose BOR is either CR or PR or SD per adapted m-RECIST and/or RECIST 1.1 criteria as assessed by BICR. BOR is determined by the best response designation recorded between the date of randomization and the date of objectively documented progression or the date of subsequent anti-cancer therapy (including tumor-directed radiotherapy, tumor-directed surgery, and systematic therapy), whichever occurs first. For subjects without documented progression or subsequent anti-cancer therapy, all available response designations will contribute to the BOR determination. For subjects

who continue study treatment beyond progression, the BOR should be determined based on response designations recorded up to the time of the initial BICR confirmed progression.

As part of the evaluation of ORR, duration of response and time to response will be evaluated. DOOR is defined as the time between the date of first response to the date of the first documented tumor progression (per adapted m-RECIST and/or RECIST 1.1 criteria) or death due to any cause. Subjects who neither progress nor die will be censored on the date of their last assessment. TTOR is defined as the time from randomization to the date of the first CR or PR. DOOR and TTOR will be evaluated for responders (CR or PR) only.

PFS as determined by BICR is defined as the time from randomization to the date of the first documented tumor progression (per adapted m-RECIST and/or RECIST 1.1 criteria) as assessed by BICR 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. Tumor assessments are scheduled to be performed at week 6 (± 7 days) from first dose date, every 6 weeks until week 48 (± 7 days) and then every 12 weeks (± 7 days) until disease progression or treatment discontinuation, whichever occurs later.

Additional secondary endpoints include PD-L1 Protein Expression level. PD-L1 expression is defined as the percent of tumor cells demonstrating plasma membrane PD-L1 staining of any intensity using the validated DAKO PD-L1 IHC assay.

[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

8.4.2.1 Primary endpoint analyses

The distribution of OS will be compared in two randomized arms at the interim and final analysis via a two-sided, log-rank test stratified by histology and gender with an overall significance level of 0.05. A group sequential testing procedure will be applied to OS to control the overall type I error for interim and final analyses. The α spending function is described in Section 8.1.The hazard ratio (HR) and the corresponding two-sided 100x (1-adjusted α) % confidence intervals (CI) will be estimated in a stratified Cox proportional hazards model using randomized arm as a single covariate. The OS curves for each randomized arm will be estimated using the Kaplan-Meier (KM) product-limit method. Two sided, 95% confidence intervals for median OS will be computed by Brookmeyer and Crowley method (using log-log transformation). Survival rates at 6, 12, 18, 24, 36, 48 months and 5 year will be estimated using KM estimates on the OS curve for each randomized arm provided minimum follow-up is longer than time-point to generate the rate. Associated two-sided 95% CIs will be calculated using the Greenwood formula (using log-log transformation).

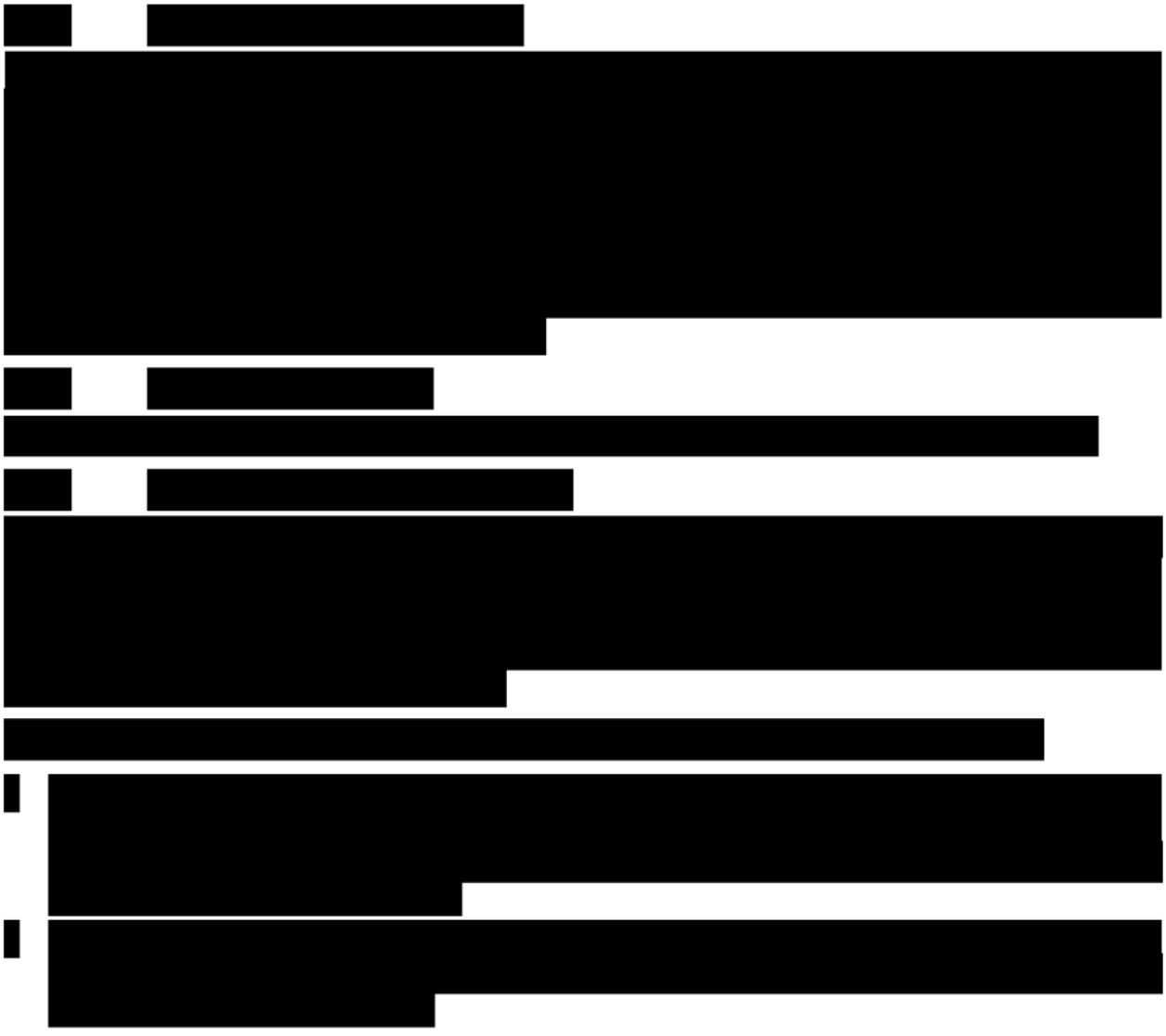
8.4.2.2 Secondary endpoints analyses

ORRs or DCRs and their corresponding 95% exact CIs will be calculated using the Clopper-Pearson method for each treatment group.

The PFS curves for each randomized arm will be estimated using the KM product-limit method. Two-sided, 95% confidence intervals for median PFS will be computed by Brookmeyer and Crowley method (using log-log transformation). PFS rates at 6, 12, 18, 24, 36, 48 months and 5 year will be estimated using KM estimates on the PFS curve for each randomized arm provided minimum follow-up is longer than timepoint to generate the rate. Associated two-sided 95% CIs will be calculated using the Greenwood formula (using log-log transformation).

8.4.3 Safety Analyses

The safety analysis will be performed in 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 by treatment arm. All on-treatment AEs, drug-related AEs, late-emergent drug-related AEs, SAEs and drug-related SAEs will be tabulated using worst Grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term. On-study lab parameters including hematology, chemistry, liver function and renal function will be summarized using worst Grade per NCI CTCAE v 4.0 criteria.



[redacted]

8.5 Interim Analyses

A formal interim analysis for the OS is planned after 403 deaths have been observed, which are expected to occur approximately 38 months after study initiation. This formal comparison of OS will allow for early stopping for superiority. Lan-DeMets α spending function with O'Brien and Fleming type of boundary will be used. The stopping boundary will depend on the actual number of deaths at the time of the interim analysis. However, if the analysis were performed exactly at 403 deaths, the study could be stopped by the DMC for superiority if the p-value is < 0.03. An independent statistician external to BMS will perform the analysis. If the study continues beyond the interim analysis the nominal significance level for the final look after 473 deaths would be 0.041. All events in the database at the time of the lock will be used. If number of final events exceeds the number specified per protocol (473 deaths), final boundary will not be recalculated using updated information fraction at interim. In addition to the formal planned interim analysis for OS, the DMC will have access to periodic unblinded interim reports of efficacy and safety to allow a risk/benefit assessment. No formal test will be performed and the study will not stop for superiority. Details will be included in the DMC charter.

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 or designee 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. Certain CRF pages and/or electronic files may serve as the source documents:

In addition, the study may be evaluated by BMS or designee 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 or designee.

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 (or head of the study site in Japan) must contact BMS or designee prior to destroying any records associated with the study.

BMS or designee 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 or designee.

9.2.2 Study Drug Records

Records for IP and non-investigational products (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.

It is the responsibility of the investigator to ensure that a current disposition record of study drug (inventoried and dispensed) is maintained at the study site to include investigational product and non-investigational product(s) 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 transferred to another area/site for dispensing or storage
- non study disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to 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.

BMS 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 Sponsor or designee 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 electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by Sponsor of designee.

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, 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 Sponsor or designee training requirements and must only access the BMS electronic data capture tool using the unique user account provided by Sponsor or designee. 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 or designee. 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 or designee 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
TNM Staging	TNM is a cancer staging system for solid tumor with numeric codes: T : indicates if the tumor is original site or has invaded nearby tissue N: indicates lymph nodes that are involved M: indicates metastasis
BRAF	BRAF is a human gene that makes a protein called B-Raf.
m-RECIST	Modified-RECIST criteria for pleural mesothelioma.

11 LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
AI	accumulation index
AI_AUC	AUC Accumulation Index; ratio of AUC(TAU) at steady state to AUC(TAU) after the first dose
AI_Cmax	Cmax Accumulation Index; ratio of Cmax at steady state to Cmax after the first dose
AI_Ctau	Ctau Accumulation Index; ratio of Ctau at steady state to Ctau after the first dose
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
APC	Antigen-Presenting Cells
AT	aminotransaminases
AUC	area under the concentration-time curve
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
AUC(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in one dosing interval
BCG	Bacillus Calmette Guerin vaccine
BICR	Blinded Independent Committee Review
BMI	body mass index
BMS	Bristol-Myers Squibb
BP	blood pressure
BRt	Total amount recovered in bile
%BRt	Total percent of administered dose recovered in bile
BUN	blood urea nitrogen
C	Celsius
C12	concentration at 12 hours
C24	concentration at 24 hours
Ca++	calcium

Term	Definition
Cavg	average concentration
CBC	complete blood count
Cexpected-tau	expected concentration in a dosing interval
CFR	Code of Federal Regulations
CI	confidence interval
C1-	chloride
CLcr	creatinine clearance
cm	centimeter
Cmax, CMAX	maximum observed concentration
Cmin, CMIN	trough observed concentration
CNS	Central nervous system
CRC	Clinical Research Center
CRF	Case Report Form, paper or electronic
Ct	Expected concentration at a certain time, usually at the end of an expected future dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
Ctau	Concentration in a dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
Ctrough	Trough observed plasma concentration
CV	coefficient of variation
CYP	cytochrome p-450
D/C	discontinue
dL	deciliter
DRt	Total amount recovered in dialysate
%DRt	Total percent of administered dose recovered in dialysate
DSM IV	Diagnostic and Statistical Manual of Mental Disorders (4th Edition)
EA	extent of absorption
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEG	electroencephalogram
eg	exempli gratia (for example)

Term	Definition
ESR	Expedited Safety Report
F	bioavailability
Fb	fraction of bound drug
FDA	Food and Drug Administration
FI	fluctuation Index ([Cmax-Ctau)/Cavg])
fu	fraction of unbound drug
g	gram
GC	gas chromatography
GCP	Good Clinical Practice
G criteria	adjusted R2 value of terminal elimination phase
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
HRT	hormone replacement therapy
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
IRB	Institutional Review Board
IU	International Unit
IV	intravenous
K	slope of the terminal phase of the log concentration-time curve

Term	Definition
K3EDTA	potassium ethylenediaminetetraacetic acid
K+	potassium
kg	kilogram
λz	terminal disposition rate constant
L	liter
LC	liquid chromatography
LCSS	Lung Cancer Symptom Scale
LCSS-Meso	Lung Cancer Symptom Scale - Mesothelioma
LDH	lactate dehydrogenase
ln	natural logarithm
Lz_Start	The time point starting the log-linear elimination Phase defining the terminal half life
Lz_End	The time point ending the log-linear elimination Phase defining the terminal half life
Lz_N	Number of time points in the log-linear elimination Phase defining the terminal half life
mg	milligram
Mg++	magnesium
MIC	minimum inhibitory concentration
min	minute
mL	milliliter
mmHg	millimeters of mercury
MPM	Malignant pleural mesothelioma
MR_AUC(0-T)	Ratio of metabolite AUC(0-T) to parent AUC(0-T), corrected for molecular weight
MR_AUC(INF)	Ratio of metabolite AUC(INF) to parent AUC(INF), corrected for molecular weight
MR_AUC(TAU)	Ratio of metabolite AUC(TAU) to parent AUC(TAU), corrected for molecular weight
MR_Cmax	Ratio of metabolite Cmax to parent Cmax, corrected for molecular weight
MR_Ctau	Ratio of metabolite Ctau to parent Ctau, corrected for molecular weight
MRT	mean residence time

Term	Definition
MS	mass spectrometry
MTD	maximum tolerated dose
µg	microgram
N	number of subjects or observations
Na+	sodium
N/A	not applicable
ng	nanogram
NSCLC	Non small cell lung cancer
pAUCe	Extrapolated partial AUC from last quantifiable concentration to infinity
Pb	percent of bound drug
PD	pharmacodynamics
PK	pharmacokinetics
Pu	percent of unbound drug
QC	quality control
R2	coefficient of determination
RBC	red blood cell
RCC	Renal cell carcinoma
SAE	serious adverse event
SD	standard deviation
SOP	Standard Operating Procedures
sp.	species
Subj	subject
t	temperature
T	time
TAO	Trial Access Online, the BMS implementation of an EDC capability
T-HALF	Half life
T-HALFeff_AUC	Effective elimination half life that explains the degree of AUC accumulation observed
T-HALFeff_Cmax	Effective elimination half life that explains the degree of Cmax accumulation observed)
Tmax, TMAX	time of maximum observed concentration
TR_AUC(0-T)	AUC(0-T) treatment ratio

Term	Definition
TR_AUC(INF)	AUC(INF) treatment ratio
TR_Cmax	Cmax treatment ratio
UV	ultraviolet
VAS	Visual Analog Scale
Vss/F (or Vss)	apparent volume of distribution at steady state
Vz	Volume of distribution of terminal phase (if IV and if multi-exponential decline)
W	washout
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
x g	times gravity

APPENDIX 1 ECOG PERFORMANCE STATUS

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

[redacted]

[redacted]

APPENDIX 3 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

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

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state 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 > 40 mIU/mL to confirm menopause.

Note: 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 judgement in checking serum FSH levels.

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

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal.

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 23 weeks after the end of study treatment.

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

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation (These methods of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited)[b] – oral (birth control pills) – intravaginal (vaginal birth control suppositories, rings, creams, gels) – transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited)[b] • Intrauterine device (IUD)[c] • Intrauterine hormone-releasing system (IUS) (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited) [b,c] • 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 treatment. 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] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study treatment, 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.

[c] 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 (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited)
- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus).
- Spermicide only
- Lactation amenorrhea method (LAM)

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILD BEARING POTENTIAL.

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP; even if the participants have undergone a successful vasectomy or if their partner is already pregnant or breastfeeding. Males should continue to use a condom while on study and for a total of 31 weeks after end of treatment (duration of sperm turnover). Withdrawal (coitus interruptus) and/or the use of a spermicide without a condom are not acceptable methods of contraception or fetal protection.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 31 weeks after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from sexual activity or use a male condom during any sexual activity (eg, vaginal, anal, oral)

even if the participants have undergone a successful vasectomy, while on study and for a total of 31 weeks after end of treatment. Withdrawal (coitus interruptus) and/or the use of a spermicide without a condom are not acceptable methods of contraception or fetal protection.

- Refrain from donating sperm for the duration of the study treatment while on study and for a total of 31 weeks after end of treatment.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.3 and the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting

APPENDIX 4 MODIFIED RECIST CRITERIA IN MALIGNANT PLEURAL MESOTHELIOMA

Malignant pleural mesothelioma and non-pleural lesions will be assessed as follows:

1 MEASUREMENT CRITERIA

1.1 Measurement of Malignant Pleural Lesions

Malignant pleural mesothelioma lesions: Recognizing that not all cases of malignant pleural mesothelioma can be assessed with six pleural measurements, the modified RECIST suggested guidance published in reference to MPM[1] has been adapted in this study to allow for the assessment of up to 6 measurements, rather than a fixed number. Response to treatment is evaluated by measuring uni-dimensional tumor thickness perpendicular to the chest wall in up to 2 positions at 3 different levels on CT. The sum of up to 6 measurements is defined as the pleural uni-dimensional measure. Each single tumor measurement must be at least 10 mm in length to qualify as measureable disease and contribute to the sum that defines the pleural uni-variate measure. The maximum number of pleural lesions, up to 6, that qualify as measurable disease must be used. Transverse cuts at least 1 cm apart and related to anatomical landmarks in the thorax are chosen to allow reproducible assessment at later time points. If a measurable tumor is present, transverse cuts in the upper thorax, above the level of the main bronchi division is preferred. At reassessment, pleural thickness is measured at the same position and at the same level by the same observer. This measurement does not necessarily represent the greatest tumor thickness at the level.

The sum of up to 6 pleural thickness measurements = one univariate diameter.

The sum of the pleural measurements is considered one target lesion.

1.2 Measurement of Non-Pleural Lesions

Non-pleural lesions: Non-pleural lesions, such as nodal, subcutaneous, and other metastatic MPM lesions, should be measured uni-dimensionally as per the RECIST 1.1 guidelines with BMS modifications. At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows:

1.2.1 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.

1.2.2 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

As noted in Section 1.1 above, the sum of the pleural measurements taken is considered one target lesion.

For non-pleural 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 EVALUATION OF LESIONS

Total Tumor Measurement: The Total Tumor Measure is equal to the sum of the Univariate Diameter (sum of up to 6 pleural thickness measurements as noted above) ***plus*** the sum of the uni-dimensional measurements of any non-pleural target lesions.

Total Tumor Measurement = Pleural lesion Univariate Diameter + Sum of non-pleural target lesions

Non-pleural and pleural solid tumors will be evaluated using Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1) guideline with BMS modifications.[2]

3 RESPONSE CRITERIA

3.1 Evaluation of Target Lesions

3.1.1 Special Notes on the Assessment 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 the Total Tumor Measurement, taking as reference the baseline sum diameters.
- **Progressive Disease (PD):** At least a 20% increase in the sum of the Total Tumor Measurement, 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 including non-pleural and pleural lesions accedded in the Total Tumor Measurement 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.

3.1.2 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.

3.1.2.1 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.

3.1.2.2 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'.

3.2 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.

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

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

3.2.2 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 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.

3.2.2.1 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.

3.2.2.2 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.

3.2.3 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.

3.3 Response Assessment

3.3.1 Time Point Response

At each protocol specified time point, a response assessment occurs. Table 3.3.1-1 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 3.3.1-2is to be used.

Table 3.3.1-1: 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
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 3.3.1-2: 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.

3.3.2 Best Overall Response

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 3.3.2-1. 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 3.3.2-1: Best Overall Response

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.

3.3.3 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]

[redacted]

[redacted]

APPENDIX 5 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

[redacted]

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 01	
Section Number & Title	**Description of Change**
Synopsis Study Design	Two-year maximum treatment duration information added with supporting data.
Synopsis Study Design	Modified Arm A to permit BICR confirmed progression according to adapted modified RECIST and/or RECIST 1.1
Synopsis Study Design	Modified schedule of on-study tumor assessments
Synopsis Study Design	Modified study schematic
Synopsis Exclusion Criteria	Certain key exclusion criteria modified
Synopsis Study Drug	Updated study drug table with additional potencies of study drugs
Synopsis Study Assessments	Updated treatment arms and procedures
Synopsis Study Endpoints	Updated secondary endpoints
Section 3.1 Study Design and Duration	Modified treatment arms A and B including addition of 2-year maximum treatment duration and chemotherapy information
Section 3.1 Study Design and Duration	Modified study schematic
Section 3.3.1 Inclusion Criteria	Clarification of tissue submission requirements
Section 3.3.1 Inclusion Criteria	Mesothelioma disease measurement updated
Section 3.3.1 Inclusion criteria 2	Radiographic assessment criteria of modified RECIST and RECIST 1.1 updated and imaging assessments were updated

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 01	
Section Number & Title	**Description of Change**
Section 3.3.2 Exclusion criteria 2	Added criteria for excluding participants with prior MPM therapy
Section 3.3.2 Exclusion criteria 2	Added criteria for excluding participants using certain herbal supplements
Section 3.4.1 Prohibited and/or Restricted Treatments	Language updated for prohibited herbal supplements,
Section 3.4.2 Other Restrictions and Precautions	Removed text permitting inhaled or topical steroids in the absence of active autoimmune disease.
Section 4 Study Drugs	Updated Table 4-1 with additional potencies of study drugs
Section 4.5 Study Drugs	Updated Table 4.5-1 footnotes
Section 4.5.1.2 Pemetrexed plus Cisplatin or Carboplatin	Modified dosing instructions for cisplatin or carboplatin in combination with pemetrexed
Section 4.5.2.1 Dose Delay Criteria for Nivolumab plus Ipilimumab	Dose delay criteria for study treatment and discontinuation criteria were updated.
Section 4.5.2.2 Dose Delay Criteria for Pemetrexed and Cisplatin or Carboplatin	Dose delay criteria for study treatment and discontinuation criteria were updated.
Section 4.5.3.2 Pemetrexed and Cisplatin or Carboplatin	Recommended audiometric testing for participants receiving cisplatin per standard of care
Section 4.5.5.1 Nivolumab Dose Discontinuation	Modified treatment discontinuation criteria for nivolumab
[redacted]	[redacted]
[redacted]	[redacted]
Section 7 Data monitoring committee and other external committees	Updated to reflect modified RECIT and RECIST 1.1 criteria

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	[redacted]
		[redacted]
[redacted]	[redacted]	[redacted]