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Ex-US Non-IND
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Clinical Protocol CA209742

Phase IIIb, Randomized, Study of Multiple Administration Regimens for Nivolumab Plus Ipilimumab in Subjects with Previously Untreated Unresectable or Metastatic Melanoma

(CheckMate 742: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 742)

Revised Protocol Number: 01
Incorporated Administrative Letters 01, 02, 03, and 04

Study Director / Medical Monitor

Fareeda Hosein, MD

[redacted]

24-hr Emergency Telephone Number

[redacted]

Bristol-Myers Squibb Research and Development

[redacted]

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.

OVERALL RATIONALE FOR THE REVISED PROTOCOL 01

[redacted].

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis 8.2 Populations for Analyses 8.3.1 Primary Endpoint(s) 8.3.2 Secondary Endpoint(s) 8.3.3 Exploratory Endpoint(s)	Changed the timing of the primary endpoint analysis	[redacted]
3.1.3 Follow-Up Phase	The study duration definition was revised	[redacted]
5.1 Flow Chart/Time and Events Schedule	"...and within 72 hours of first dose" was removed from the vital signs row in Table 5.1-1 Screening Procedural Outline (CA209742)	On-study assessments are captured on Tables 5.1-2 and 5.1-3.
5.1 Flow Chart/Time and Events Schedule	"...or serum urea level" was added to the list of laboratory tests	Inclusion of serum urea level is consistent with Section 5.3, Safety Assessments.

Minor corrections (eg, typographical errors, formatting, and word choices) were incorporated.

SYNOPSIS

Clinical Protocol CA209742

Protocol Title: Phase IIIb, Randomized, Study of Multiple Administration Regimens for Nivolumab Plus Ipilimumab in Subjects with Previously Untreated Unresectable or Metastatic Melanoma

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

This is a Phase IIIb, open-label, randomized 2-arm study of the Fixed Ratio Combination product of nivolumab and ipilimumab in a 1:3 ratio (BMS-986214):

Part 1:

- In Arm A, BMS-986214 will be administered as one 60 minute infusion. Subjects will receive a total of four doses in Part 1
- In Arm B, nivolumab and ipilimumab will be administered sequentially, as two separate infusions, one 60 minute nivolumab infusion and one 90 minute ipilimumab infusion with a 30 minute break between each infusion
- Note: Cycles will be defined as three weeks in the combination period, Part 1

Part 2:

- Six weeks after the administration of the last combination dose in Part 1, subjects will then receive nivolumab flat dose (480mg, 30 minute infusion) every four weeks in Part 2 until progression or unacceptable toxicity (total maximum treatment duration up to 2 years)
- Note: Cycles will be defined as four weeks in the flat dosing period, Part 2

Study Phase: Phase IIIb

Research Hypothesis: Treatment with BMS-986214 will demonstrate no clinically relevant differences in safety relative to nivolumab and ipilimumab administered sequentially in patients with previously untreated, unresectable, or metastatic melanoma.

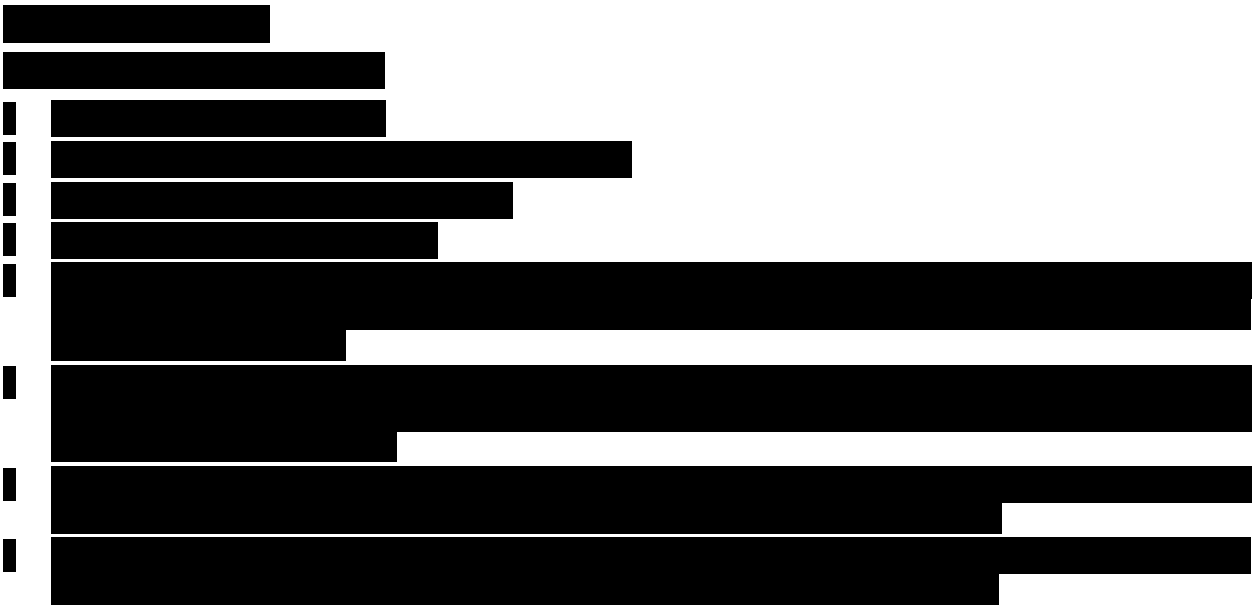
Objectives:

Primary Objective

The primary objective is to evaluate the difference in safety between the FRC product (BMS-986214) relative to sequentially administered nivolumab 1 mg/kg and ipilimumab 3 mg/kg as measured by the incidence of AEs in the Broad Scope MedDRA Anaphylactic Reaction SMQ occurring within 2 days after dosing during the combination, Part 1 period in subjects with previously untreated, unresectable or metastatic melanoma.

Key secondary objectives include:

- To evaluate incidence of AEs in the Narrow Scope MedDRA Anaphylactic Reaction SMQ and the select AE hypersensitivity/infusion reaction category
- To evaluate Grade 3 - 5 AE incidence rate (drug-related and all causality) defined using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0 criteria
- To determine PK comparisons of nivolumab and ipilimumab administered as FRC to that of sequentially administered nivolumab and ipilimumab
- To evaluate the objective response rate (ORR), as determined by investigators
- To evaluate progression free survival (PFS)



Study Design:

This is a Phase IIIb, open-label, randomized 2-arm study of the Fixed Ratio Combination product of nivolumab and ipilimumab in a 1:3 ratio (BMS-986214).

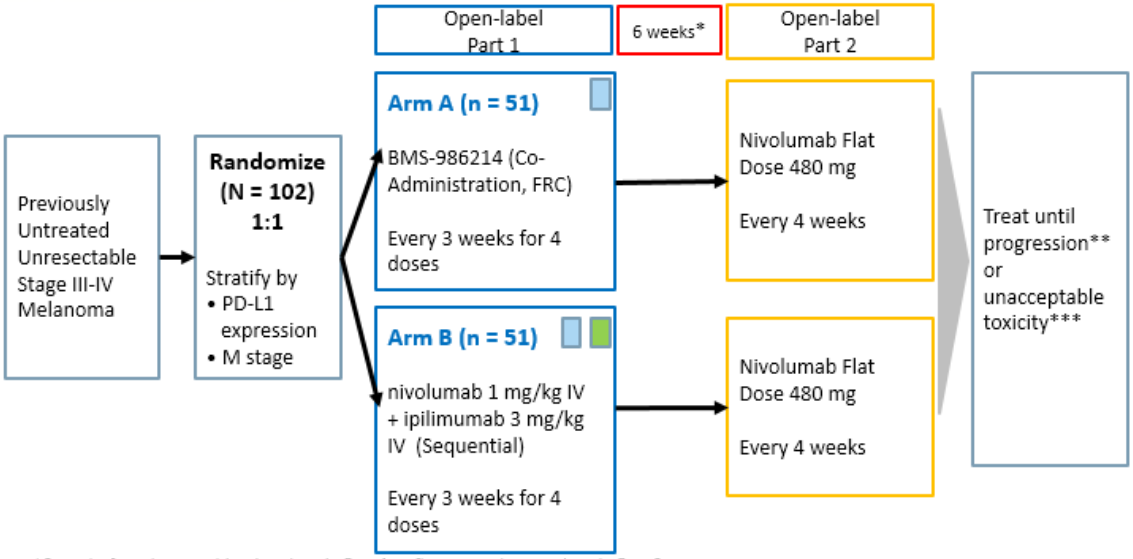
In Arm A, BMS-986214 will be administered as one 60 minute infusion. Subjects will receive a total of four doses in Part 1.

In Arm B, nivolumab and ipilimumab will be administered sequentially, as two separate infusions, one 60 minute nivolumab infusion and one 90 minute ipilimumab infusion with a 30 minute break between each infusion.

Six weeks after the administration of the last combination dose in Part 1, subjects will then receive nivolumab flat dose (480 mg, 30 minute infusion) every four weeks in Part 2 until progression or unacceptable toxicity (total maximum treatment duration up to 2 years).

The study population for this trial will include male and female patients ≥ 15 years of age (except where local regulations and/or institutional policies do not allow for subjects < 18 years of age (pediatric population) to participate. For those sites, the eligible subject population is ≥ 18 years) with previously untreated, unresectable or metastatic melanoma. Subjects must have unresectable or metastatic Stage III or Stage IV melanoma, as per the AJCC staging system and must not have received prior systemic therapy for the treatment of unresectable or metastatic melanoma. The study design schematic is presented in the figure below. The duration of the trial is expected to be 6 months of accrual and approximately 60 months of follow-up after the last patient has received the first dose.

Subjects who advance to Part 2 will be treated until progression or unacceptable toxicity (total maximum treatment duration up to 2 years).



*6 weeks from last combination dose in Part 1 to first monotherapy dose in Part 2
**Treatment beyond initial investigator-assessed RECIST 1.1-defined progression will be considered in subjects experiencing investigator assessed clinical benefit and tolerating study therapy. Such subjects must discontinue therapy when further progression is documented.
***Subjects who advance to Part 2 will be treated until progression or unacceptable toxicity (total maximum treatment duration up to 2 years including Part 1 and Part 2)

Study Population:

Inclusion:

- Males and Females, ages ≥ 15 years of age
    - Except where local regulations and/or institutional policies do not allow for subjects < 18 years of age (pediatric population) to participate. For those sites, the eligible subject population is ≥ 18 years of age
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-1
- No prior systemic anticancer therapy for unresectable or metastatic melanoma. Prior adjuvant or neoadjuvant melanoma therapy is permitted if it was completed at least 6 weeks prior to date of first dose, and all related adverse events have either returned to baseline or stabilized
- Measurable disease as per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST) criteria
- Tumor tissue from an unresectable or metastatic site of disease must be provided for biomarker analyses. In order to be randomized, a subject must have quantifiable PD-L1 expression (≥ 5% or < 5% tumor cell membrane staining) or be classified as PD-L1 indeterminate. Tumor PD-L1 expression will be centrally assessed prior to patient randomization
    - If an insufficient amount of tumor tissue from an unresectable or metastatic site is available prior to the start of the screening phase, subjects must consent to allow the acquisition of additional tumor tissue for performance of biomarker analyses
- Known BRAF V600 mutation status as determined by local institutional standard or subject to consent to BRAF V600 mutation testing per local institutional standards during the Screening Period, the results of which must be reported within 3 months of randomization. All BRAF statuses (BRAF wild-type or BRAF 600 mutation positive) are eligible

Exclusion:

- Active brain metastases or leptomeningeal metastases. Subjects with brain metastases are eligible if these have been treated and there is no magnetic resonance imaging (MRI -except where contraindicated in which CT scan is acceptable) evidence of progression for at least 8 weeks after treatment is complete and within 28 days prior to

first dose of study drug administration. There must also be no requirement for high doses of systemic corticosteroids that could result in immunosuppression (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration

- Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast
- Ocular melanoma
- Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll

Subjects must also meet the study criteria including exclusion for medical history, positive hepatitis B/C, HIV and pregnancy tests, and the specified laboratory criteria.

Study Drug:

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

Product Description/Class and Dosage Form	Potency	Primary Packaging (Volume)/Label Type
Nivolumab Solution for Injection[a]	100 mg (10 mg/mL) or 40 mg (10 mg/mL)	10 mL per vial Or 4 mL vial/Open label
Ipilimumab	200 mg (5 mg/mL)	40 mL per vial/Open-label
BMS-986214 Solution for Injection (Nivolumab/Ipilimumab FRC)	40 mg Nivolumab 120 mg Ipilimumab	26 mL vial/Open-label

[a] Nivolumab is labeled as BMS-936558-01 Solution for Injection

Study Assessments:
The study consists of three phases: Screening, Treatment and Follow-up. The treatment phase is divided in two parts: Part 1 consists of BMS-986214 or nivolumab 1mg/kg and ipilimumab 3 mg/kg (sequential) and Part 2 that consists in monotherapy by nivolumab 480 mg flat dose. It is anticipated that 100 patients with previously untreated, unresectable or metastatic melanoma subjects will be treated for the entire study.

All subjects will undergo a screening period to determine eligibility within 28 days prior to initial dosing. During Part 1of treatment phase, the subject will receive intravenous infusion of nivolumab and ipilimumab every 3 weeks, for a total of four doses. During Part 2 of the treatment phase starting six weeks after Part 1 ends, patients will receive 480 mg nivolumab flat dose intravenously every 4 weeks until progression or unacceptable toxicity (total maximum duration up to 2 years).

Safety of subjects will be monitored on an ongoing basis by the study team. The BMS medical monitor is a physician who is responsible for reviewing the safety of patients in this study in a systematic and continuous manner. This includes a review of serious and non-serious adverse events including all hematological and non-hematological events.

In addition, study safety is evaluated on an ongoing basis by representatives of BMS Global Pharmacovigilance and the BMS medical safety team (MST), who operate independently from the clinical team and monitor safety across all nivolumab protocols, identify potential safety signals, notify appropriate stakeholders of relevant findings, and implement risk management plans.

Statistical Considerations:

Sample Size:

Approximately 102 subjects will be randomized to the 2 treatment arms in a 1:1 ratio in order to target 100 treated subjects (50 per arm). This number of treated subjects was chosen to achieve a sufficient level of precision for a descriptive analysis to estimate the difference in rates of AEs in the Broad Scope MedDRA Anaphylactic Reaction SMQ between the two treatment arms. Fifty treated subjects per arm will allow estimation of the rate difference within 95% confidence limits of +/- 20% or less and will be supplemented by a qualitative clinical assessment of the type and severity of events to evaluate benefit-risk.

In previously submitted Phase 2/3 studies of nivolumab in combination with ipilimumab (CA209069 and CA209067), AEs in the MedDRA Anaphylactic Reaction SMQ (broad scope) with onset within 2 days after sequential dosing of nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg were reported in 24% of treated subjects. In the current study, if the observed rate of these events is equal to 24% among 50 treated subjects in each arm, then the 95% CI for the difference in rates between arms will be (-16.7%, 16.7%).

Endpoints:

The primary endpoint of the study is the incidence of AEs in the Broad Scope MedDRA Anaphylactic Reaction SMQ reported within 2 days after dosing during the combination, Part 1 period. This incidence rate is defined as number of subjects who experienced at least 1 AE in the MedDRA Anaphylactic Reaction broad scope SMQ with onset on the day of or within 2 days after any study therapy infusion during the combination period (Part 1) divided by number of treated subjects.

The analysis of the primary endpoint will occur at the time of first (primary) analysis when all subjects who are still on-treatment have completed the Part 1 period.

The secondary endpoints of the study are as follows:

- Incidence of AEs in the MedDRA Anaphylactic Reaction narrow scope SMQ occurring within 2 days after any study therapy infusion during the combination, Part 1 period
- Incidence of events within the hypersensitivity/infusion reaction select AE category occurring within 2 days after any study therapy infusion during the combination, Part 1 period
- Grade 3 - 5 AE incidence rate (drug-related and all causality) defined using NCI CTCAE version 4.0 criteria
- PK comparisons of nivolumab and ipilimumab administered as FRC DP to that of sequentially administered nivolumab and ipilimumab
- ORR as determined by investigators. The ORR is defined as the number of subjects with a BOR of CR or PR divided by the number of treated subjects for each treatment group
- PFS

Safety- and PK-related secondary endpoints will be analyzed at the time of the first (primary) analysis when all subjects who are still on-treatment have completed the Part 1 period. Efficacy-related secondary endpoints will be analyzed at the time of final analysis when all subjects have had at least 9 months of follow-up.

Analyses:

For the primary analysis, the incidence of AEs in the Broad Scope MedDRA Anaphylactic Reaction SMQ occurring within 2 days after any dose in Part 1 dosing by treatment arm, the difference in rates between arms, and the corresponding 95% confidence intervals will be reported descriptively. The confidence intervals for the rate estimates will be based on the Clopper and Pearson method. The estimate and confidence interval for the rate difference will be based on CMH method of weighting, adjusting for PD-L1 status and M Stage at screening. Descriptive statistics will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 by treatment group. Events will be tabulated using worst grade per NCI CTCAE v 4.0 criteria by preferred term.

Secondary endpoints of anaphylactic reactions based on MedDRA narrow scope SMQ and hypersensitivity/infusion reaction select AEs will be summarized using the same methods as described above for the primary endpoint analysis. On-treatment drug-related and all causality Grade 3 - 5 AEs will be tabulated using worst grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term by treatment arm.

PK will be summarized using non-compartmental analyses. ORRs and corresponding 95% exact CIs will be calculated using the Clopper Pearson method for each of the treatment arms. BOR will be tabulated for each treatment group. Associated odds ratios and 95% CIs for Arm A relative to Arm B will be calculated. An estimate of the difference in ORRs and corresponding 95% CI will be calculated using CMH methodology, adjusting for the stratification factors PD-L1 expression and M stage at screening. PFS curves for each treatment group will be estimated using the Kaplan-Meier (KM) product limit method. Median PFS and corresponding two-sided, 95% confidence intervals will be computed. Descriptive HRs and corresponding two sided 95% CIs for Arm A relative to Arm B will be estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by PD-L1 status and M Stage at screening.

TABLE OF CONTENTS

[redacted]

1.2 Research Hypothesis

Treatment with BMS-986214 will demonstrate no clinically relevant differences in safety relative to nivolumab and ipilimumab administered sequentially in patients with previously untreated, unresectable, or metastatic melanoma.

1.3 Objectives(s)

1.3.1 Primary Objectives

The primary objective is to evaluate the difference in safety between co-administered FRC nivolumab 1 mg/kg and ipilimumab 3 mg/kg relative to sequentially administered nivolumab 1 mg/kg and ipilimumab 3 mg/kg as measured by the incidence of AEs in the Broad Scope MedDRA Anaphylactic Reaction SMQ occurring within 2 days after dosing during the combination, Part 1 period in subjects with previously untreated, unresectable or metastatic melanoma.

1.3.2 Secondary Objectives

- To evaluate incidence of AEs in the Narrow Scope MedDRA Anaphylactic Reaction SMQ and the select AE hypersensitivity/infusion reaction category
- To evaluate Grade 3 - 5 AE incidence rate (drug-related and all causality) defined using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0 criteria
- To determine PK comparisons of nivolumab and ipilimumab administered as FRC to that of sequentially administered nivolumab and ipilimumab
- To evaluate the objective response rate (ORR), as determined by investigators
- To evaluate progression free survival (PFS)

[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 Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50) and applicable local requirements.

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

All potential serious breaches must be reported to 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

This is a Phase IIIb, open-label, randomized 2-arm study of the Fixed Ratio Combination product (BMS-986214).

In Arm A, BMS-986214 will be administered as one 60 minute infusion. Subjects will receive a total of four doses in Part 1.

In Arm B, nivolumab and ipilimumab will be administered sequentially, as two separate infusions, one 60 minute nivolumab infusion and one 90 minute ipilimumab infusion with a 30 minute break between each infusion.

Six weeks after the administration of the last combination dose in Part 1, subjects will then receive nivolumab flat dose (480 mg, 30 minute infusion) every four weeks in Part 2 until progression or unacceptable toxicity (total maximum treatment duration up to 2 years including Part 1 and Part 2).

Safety of subjects will be monitored on an ongoing basis by the study team. The BMS medical monitor is a physician who is responsible for reviewing the safety of patients in this study in a systematic and continuous manner. This includes a review of serious and non-serious adverse events including all hematological and non-hematological events.

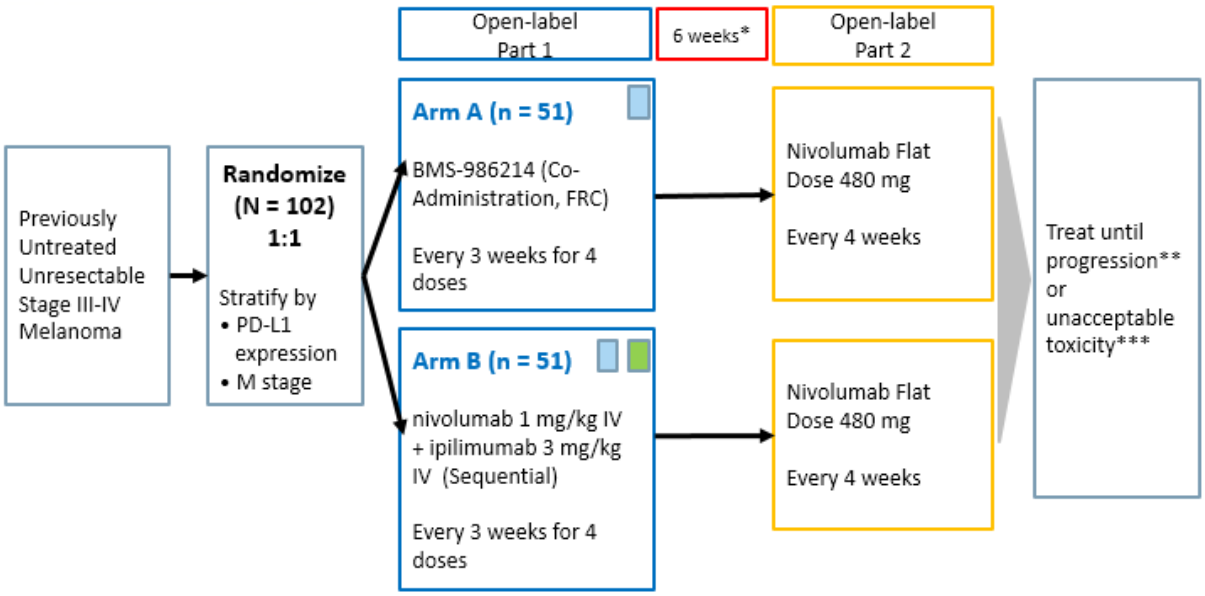
In addition, study safety is evaluated on an ongoing basis by representatives of BMS Global Pharmacovigilance and the BMS medical safety team (MST), who operate independently from the clinical team and monitor safety across all nivolumab protocols, identify potential safety signals, notify appropriate stakeholders of relevant findings, and implement risk management plans.

The study population for this trial will include male and female patients ≥ 15 years of age (except where local regulations and/or institutional policies do not allow for subjects < 18 years of age (pediatric population) to participate. Preliminary analysis of a pediatric nivolumab study also indicated that nivolumab exposure (observed trough concentrations after the 1st dose) was similar between pediatric (age 6 to 12 yr) and adult patients. For those sites, the eligible subject population is ≥ 18 years) with previously untreated, unresectable or metastatic melanoma. Subjects must have unresectable or metastatic Stage III or Stage IV melanoma, as per the AJCC staging system and must not have received prior systemic therapy for the treatment of unresectable or metastatic melanoma. The study design schematic is presented in the figure below. The duration of the trial is expected to be 6 months of accrual and approximately 60 months of follow-up after the last patient has been dosed.

Subjects who advance to Part 2 will be treated until progression or unacceptable toxicity (total maximum treatment duration up to 2 years including Part 1 and Part 2).

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

Figure 3.1-1: Study Design Schematic



*6 weeks from last combination dose in Part 1 to first monotherapy dose in Part 2
**Treatment beyond initial investigator-assessed RECIST 1.1-defined progression will be considered in subjects experiencing investigator assessed clinical benefit and tolerating study therapy. Such subjects must discontinue therapy when further progression is documented.
***Subjects who advance to Part 2 will be treated until progression or unacceptable toxicity (total maximum treatment duration up to 2 years including Part 1 and Part 2)

The start of the trial is defined as the first visit for the first subject screened. The end of the trial is defined as the last scheduled procedure shown in the time and events schedule for the last subject. Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected, if this is not the same.

This study will consist of 3 phases: screening, treatment, and follow-up.

3.1.1 Screening Phase

- Begins by establishing the subject's initial eligibility and signing of the ICF
- Subject is enrolled using the Interactive Response Technology (IRT)
- Tumor tissue obtained in the metastatic setting or from an unresectable site of disease must be provided for biomarker analyses. In order to be randomized, a subject must have quantifiable PD-L1 expression (≥ 5% or < 5% tumor cell membrane staining) or be classified as PD-L1 indeterminate. If an insufficient amount of tumor tissue from an unresectable or metastatic site is available prior to the start of the screening phase, subjects must consent to the acquisition of additional tumor tissue for performance of biomarker analyses

3.1.2 Treatment Phase

- Begins with the randomization call to the IRT

- Subject will be randomized to:
  - (Arm A) BMS-986214 will be administered as one 60 minute infusion. Subjects will receive a total of four doses in Part 1
  - (Arm B) nivolumab and ipilimumab will be administered sequentially, as two separate infusions, one 60 minute nivolumab infusion and one 90 minute ipilimumab infusion with a 30 minute break between each infusion
- All subjects randomized to Arm B should receive both nivolumab and ipilimumab throughout Part 1, and decisions to discontinue study drug therapy must include both nivolumab and ipilimumab. It is not permitted to continue nivolumab without ipilimumab
- After combination therapy, all subjects will receive a flat dose 480 mg nivolumab 30 minute infusion every 4 weeks, beginning 6 weeks after the last combination dose, until progression or unacceptable toxicity (total maximum treatment duration up to 2 years including Part 1 and Part 2)
- For WOCBP, a negative pregnancy test should be documented within 24 hours prior to start of each dose of investigational product
- Within 3 working days from randomization, the subject must receive the dose of study medication
- On study laboratory assessments should be drawn within 72 hours prior to dosing
- PK samples and immunogenicity samples will be collected according to the schedule in Table 5.1-2, Table 5.1-3, and Table 5.1-4
- Adverse event assessments should be documented at each clinic visit
- Quality of Life will be assessed using EORTC QLQ-C30 and EQ-5D-3L questionnaires, to be completed after randomization, prior to the first dose of study therapy and according to the schedule in Section 5.1
- Study drug dose may be delayed for toxicity. See Section 4.5.1
- Treated subjects will be evaluated for response according to the RECIST 1.1 guidelines beginning 12 weeks (± 1 week) after randomization and continuing every 8 weeks (± 1 week) for the first 12 months, and then every 12 weeks (± 2 week) until disease progression or treatment discontinuation, whichever occurs later
- This phase ends when the subject is discontinued from study therapy. For a complete list of reasons for treatment discontinuation, see Section 3.5

3.1.3 Follow-Up Phase

- Begins when the decision to discontinue a subject from study therapy is made (no further treatment with study therapy). Patients will be followed for efficacy and OS
- Subjects who discontinue treatment for reasons other than tumor progression will continue to have tumor assessments beginning 12 weeks (± 1 week) after randomization and continuing every 8 weeks (± 1 week) for the first 12 months from randomization, and every 12 weeks (± 2 weeks) thereafter until documented tumor progression

- 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 last dose
- After completion of the first two follow-up visits, subjects will be followed every 3 months for survival
- BMS may request that survival data be collected on all randomized subjects outside of the protocol defined window as detailed in the Time and Events Table 5.1-4 Follow-up Assessments (CA209742). At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contact

The duration of the study from start of randomization to first (primary) analysis of the study is expected be approximately 10 months (7 months of accrual plus approximately an additional 3 months to ensure all subjects who are still on-treatment have completed the Part 1 period). The duration of the study from start of randomization to final analysis of the study is expected be approximately 16 months (7 months of accrual plus an additional 9 months to ensure all subjects have at least 9 months of follow-up).The study will have an accrual rate of approximately 17 subjects treated per month. Additional survival follow-up may continue for up to 5 years from the primary analysis. The study will end once survival follow-up has concluded.

3.2 Post Study Access to Therapy

At the end of the study treatment period (total maximum treatment duration up to 2 years including Part 1 and Part 2), BMS will not continue to provide BMS supplied study drug to subjects/investigators unless BMS chooses to extend the study. The investigator should ensure that the subject receives appropriate standard of care to treat the condition under study.

3.3 Study Population

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

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

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

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

2. Target Population

a) Histologically confirmed melanoma (per AJCC staging system) that is unresectable or metastatic (Refer to Appendix 4)

b) Eastern Cooperative Oncology Group (ECOG) performance status of 0-1

c) No prior systemic anticancer therapy for unresectable or metastatic melanoma. Prior adjuvant or neoadjuvant melanoma therapy is permitted if it was completed at least 6 weeks

prior to date of first dose, and all related adverse events have either returned to baseline or stabilized

d) Measurable disease by CT or MRI per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST) criteria

e) Tumor tissue from an unresectable or metastatic site of disease must be provided for biomarker analyses. In order to be randomized, a subject must have quantifiable PD-L1 expression (≥ 5% or < 5% tumor cell membrane staining) or be classified as PD-L1 indeterminate. Tumor PD-L1 expression will be centrally assessed prior to patient randomization

   i) If an insufficient amount of tumor tissue from an unresectable or metastatic site is available prior to the start of the screening phase, subjects must consent to allow the acquisition of additional tumor tissue for performance of biomarker analyses

f) Known BRAF V600 mutation status as determined by local institutional standard or subject to consent to BRAF V600 mutation testing per local institutional standards during the Screening Period, the results of which must be reported within 3 months of randomization. All BRAF statuses (BRAF wild-type or BRAF 600 mutation positive) are eligible

g) Prior radiotherapy must have been completed at least 2 weeks prior to study drug administration

h) Screening laboratory values must meet the following criteria (using CTCAE v4):

   i) WBC ≥ 2000/uL

   ii) Neutrophils ≥ 1500/uL

   iii) Platelets ≥ $100x10^3$/uL

   iv) Hemoglobin ≥ 9.0 g/dL

   v) Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or calculated creatinine clearance > 40 mL/min (using the Cockcroft Gault formula):

   $$\text{Female CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/ dL}}$$

   $$\text{Male CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/ dL}}$$

   vi) AST ≤ 3.0 x ULN

   vii) ALT ≤ 3.0 x ULN

   viii) Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome who must have a total bilirubin level of < 3.0x ULN)

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

3. Age and Reproductive Status

a) Males and Females, ages ≥ 15 years of age

   i) Except where local regulations and/or institutional policies do not allow for subjects < 18 years of age (pediatric population) to participate. For those sites, the eligible subject population is ≥ 18 years of age

b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug. Women must not be breastfeeding

c) Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception, as indicated in the informed consent form, for a period of 30 days (duration of ovulatory cycle) plus the time required for the investigational drug to undergo approximately five half-lives. WOCBP should therefore use an adequate method to avoid pregnancy for 5 months (30 days plus the time required for nivolumab to undergo approximately five half lives) after the last dose of investigational drug (combination or monotherapy).

d) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception, as indicated in the informed consent form, for a period of 90 days plus the time required for the investigational drug to undergo approximately five half-lives. Men who are sexually active with WOCBP must continue contraception for 7 months (90 days plus the time required for nivolumab to undergo approximately five half-lives) after the last dose of investigational drug (combination or monotherapy). In addition, male subjects must be willing to refrain from sperm donation during this time.

e) 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. Investigators shall advise on the use of highly effective methods of contraception (Appendix 5), which have a failure rate of < 1% when used consistently and correctly.

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Active brain metastases or leptomeningeal metastases. Subjects with brain metastases are eligible if these have been treated and there is no magnetic resonance imaging (MRI - except where contraindicated in which CT scan is acceptable) evidence of progression for at least 8 weeks after treatment is complete and within 28 days prior to first dose of study drug administration. There must also be no requirement for high doses of systemic corticosteroids that could result in immunosuppression (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.

b) Ocular melanoma

2. Medical History and Concurrent Diseases

a) Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast

b) Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring

hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

c) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways

d) Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at sites where mandated locally

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

f) Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the subject to receive protocol therapy, or interfere with the interpretation of study results

3. Physical and Laboratory Test Findings

a) Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic infection, and/or detectable virus

4. Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to 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.

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]

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 intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject

- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness

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.

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

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

BMS may request that survival data be collected on all 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, listed in Table 4-1:

Table 4-1: Study Drugs for CA209742

Product Description/Class and Dosage Form	Potency	Primary Packaging (Volume)/Label Type	Secondary Packaging (Qty)/Label Type	Packaging/ Appearance	Storage Conditions (per label)
Nivolumab Solution for Injection[a]	**100 mg (10 mg/mL) or** 40 mg (10 mg/mL)	**10 mL per vial Or** 4 mL vial/Open label	**5 or 10 vials per carton/ Open-label Or 240 mg kits (2-100 mg vials and 1-40 mg vial)**	Clear to slightly opalescent, colorless to pale yellow liquid. Light (few) particulates may be present.	2° to 8 °C. Protect from light and freezing
Ipilimumab	200 mg (5 mg/mL)	40 mL per vial/Open-label	4 vials per carton/Open-label	Clear to slightly opalescent, colorless to pale yellow liquid. Light (few) particulates may be present.	2° to 8 °C. Protect from light and freezing
BMS-986214 Solution for Injection (Nivolumab/Ipilimumab FRC)	40 mg Nivolumab/ 120 mg Ipilimumab	26 mL vial/Open-label	6 vials per carton/Open-label	Clear to opalescent, colorless to pale yellow liquid. Light (few) particulates may be present	2° to 8 °C. Protect from light and freezing

[a] Nivolumab is labeled as BMS-936558-01 Solution for Injection

The fixed ratio combination drug product is formulated by combining the nivolumab drug substance and ipilimumab drug substance at a nivolumab/ipilimumab protein-mass ratio of 1 to 3. The composition and manufacturing process of these 2 drug substances are the same as those used for the nivolumab and ipilimumab commercial drug products.

The Sponsor has conducted quality testing to demonstrate that no interaction occurs between the two antibodies. Table 4-2 provides the composition of the three products.

Table 4-2: Study Drug Composition for CA209742

Component	Nivolumab	Ipilimumab	Fixed Ratio Combination
Nivolumab	10 mg/mL		1.54 mg/mL
Ipilimumab		5 mg/mL	4.62 mg/mL
Sodium Citrate	20 mM		1.54 mM
Tris Hydrochloride		20 mM	18.46 mM
Sodium Chloride	50 mM	100 mM	96.15 mM
Mannitol	3%	1%	1.15%
Pentetic Acid	20 µM	100 µM	93.85 µM
Polysorbate 80	0.02% w/v	0.01% w/v	0.012% w/v

4.1 Investigational Product

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

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

- Nivolumab
- Ipilimumab
- BMS-986214 (Nivolumab/Ipilimumab 1:3)

4.2 Non-investigational Product

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

4.3 Storage of Study Drug

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

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

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

4.3.1 Part 1 Study Drug Administration

In Part 1 of the study there will be two treatment arms:

Arm A BMS-986214 will be administered as one 60 minute infusion on Day 1 of each treatment cycle every 3 weeks for 4 doses or until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.

Arm B nivolumab and ipilimumab will be administered sequentially, as two separate infusions, one 60 minute nivolumab infusion and one 90 minute ipilimumab infusion with a 30 minute break between each infusion. Nivolumab is to be administered first. Subjects should receive nivolumab at a dose of 1 mg/kg (Arm B) as a 60-minute IV infusion, on Day 1 of each treatment cycle every 3 weeks for 4 doses or until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.

The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the next infusion.

The second infusion will always be ipilimumab, and the time in between infusions is expected to be approximately 30 minutes but may be more or less depending on the situation. Subjects should receive ipilimumab at a dose of 3 mg/kg as a 90-minute IV infusion, on Day 1 of each treatment cycle every 3 weeks for 4 doses or until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.

The risk/benefit profile for nivolumab has primarily been investigated using a 60-minute infusion and for ipilimumab a 90-minute infusion. Previous clinical studies of nivolumab have used 60-minute infusion duration and for ipilimumab 90-minute. Both nivolumab and ipilimumab have been administered safely at doses ranging up to 10 mg/kg over these infusion durations. Overall, infusion reactions including high-grade hypersensitivity reactions have been uncommon across multiple clinical studies, and all have been managed by following the safety algorithms.

Both agents given as single agent is uncommonly associated with infusion reactions, incidence less than 1% for ipilimumab (Yervoy® FDA Label) and for nivolumab 3%.[14] In the CA209069 study, hypersensitivity/infusion reactions were listed as 3.2% for the combination and 2.2% for ipilimumab. No Grade 3 or Grade 4 hypersensitivity/infusion reactions were observed in either the combination or single agent ipilimumab treatment groups.[32]

Subjects should be carefully monitored for infusion reactions during study drug administration. If an acute infusion reaction is noted, subjects should be managed according to Section 4.5.6.

The **pharmacy manual** includes detailed instructions for study medication preparation.

Dosing calculations should be based on the body weight assessed at screening. It is not necessary to re-calculate subsequent doses if the subject weight is within 10% of the weight used to calculate the previous dose. All doses should be rounded to the nearest milligram.

During Part 1, subjects may be dosed no less than 19 days between doses. If dosing is delayed, both nivolumab and ipilimumab must be delayed together. If dosing is resumed after a delay, both nivolumab and ipilimumab must be resumed on the same day.

Detailed instructions for dilution and infusion of study drug injection may be provided in the pharmacy binder, pharmacy reference sheet or current investigator brochures.[31,33] Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

4.3.2 Part 2 Study Drug Administration

Starting 6 weeks after the last co-administered dose in Part 1, subjects will be administered a flat dose 480 mg nivolumab 30 minute infusion every 4 weeks (Q4W) until unacceptable toxicity or disease progression (total maximum treatment duration up to 2 years including Part 1 and Part 2).

Subjects may be dosed up to 3 days after the scheduled date if necessary. Subsequent dosing should be based on the actual date of administration of the previous dose of drug. Every effort should be made to adhere to protocol treatment schedule of administration of nivolumab every 4 weeks in the maintenance phase. In extenuating circumstances in which the patient cannot make the dosing schedule within the 3-day window, BMS Monitor should be contacted.

For details on prepared drug storage, preparation, and administration, please refer to the nivolumab, ipilimumab and BMS-986214 IBs and/or pharmacy reference sheets.

4.4 Method of Assigning Subject Identification

CA209742 is a randomized study. After the subject's initial eligibility is established and informed consent has been obtained, the subject must be enrolled into the study by accessing an Interactive Response Technologies web-based system (IRT) to obtain the subject number. Every subject that signs the informed consent form must be assigned a subject number in IRT. Specific instructions for using IRT will be provided to the investigational site in a separate document. The investigator or designee will register the subject for enrollment by following the enrollment procedures established by BMS. The following information is required for enrollment:

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

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

- Subject number
- Date of birth
- PD-L1 expression level (PD-L1 ≥ 5% expression vs PD-L1 < 5% expression/indeterminate) entered by vendor
- M Stage at screening (M0/M1a/M1b vs. M1c) (See Appendix 4).

Subjects meeting all eligibility criteria will randomize 1:1 ratio to Arm A or Arm B and stratified by the following factors:

- PD-L1 expression
- M stage.

The randomization procedures will be carried out via permuted blocks within each stratum. The exact procedures for using the IRT will be detailed in the IRT manual.

4.5 Selection and Timing of Dose for Each Subject

Note: The first flat dose 480 mg nivolumab in Part 2 will be administered 6 weeks after the last dose in Part 1.

Table 4.5-1: Dosing Schedule for Part 1 (Open Label)

Every 3 weeks dosing 1 cycle = 3 weeks				
	Cycle 1	**Cycle 2**	**Cycle 3**	**Cycle 4**
Arm A	BMS-986214	BMS-986214	BMS-986214	BMS-986214
Arm B	Nivolumab 1 mg/kg Ipilimumab 3 mg/kg	Nivolumab 1 mg/kg Ipilimumab 3 mg/kg	Nivolumab 1 mg/kg Ipilimumab 3 mg/kg	Nivolumab 1 mg/kg Ipilimumab 3 mg/kg

Table 4.5-2: Dosing Schedule for Part 2 (Open Label)

Every 4 weeks dosing 1 cycle = 4 weeks Cycle 5 begins six weeks after cycle 4 starts, or 3 weeks after cycle 4 ends since each of the first 4 cycles is 3 weeks	
	Cycle 5 and beyond
Arms A and B	Flat dose 480 mg nivolumab

When 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 patient 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.

There will be no dose escalations or reductions of study drug allowed. For Q4W dosing cycles, subjects may be dosed within a +/- 3 day window. Premedications are not recommended for the first dose of nivolumab.

Subjects should be carefully monitored for infusion reactions during study drug administration. If an acute infusion reaction is noted, subjects should be managed according to Section 4.5.6.

Doses of nivolumab, ipilimumab, and BMS-986214 may be interrupted, delayed, or discontinued depending on how well the subject tolerates the treatment. Dosing visits are not skipped, only delayed.

Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding (polyethersulfone membrane) in-line filter at the protocol specified doses and infusion times. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 0.35 mg/mL. During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Instructions for dilution and infusion of nivolumab injection may be provided in the clinical protocol, pharmacy binder, pharmacy manual, 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. Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles. Vials of nivolumab injection must be stored at 2°C to 8°C (36°F to 46°F) and protected from light and freezing.

Ipilimumab injection can be used for IV administration without dilution after transferring to a PVC, non-PVC/non-DEHP or glass container and is stable for 24 hours at 2-8°C or room temperature/room light (RT/RL). 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.

Ipilimumab is to be administered as a ~90 minute IV infusion, using a volumetric pump with a 0.2 to 1.2 micron in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% normal saline or 5% Dextrose Injection to concentrations between 1 mg/mL and 4 mg/mL. It is not to be administered as an IV push or bolus injections. 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.

BMS-986214 injection is to be administered as an IV infusion through a 0.2-micron pore size, low-protein binding in-line filter at the protocol-specified doses and infusion times. It is not to be administered as an IV push or bolus injection. Prior to infusion, the BMS-986214 injection is diluted with 0.9% Sodium Chloride Injection, United States Pharmacopeia (USP) to required concentrations.

BMS-986214 is available as a solution at a concentration of 6.2 mg/ml. The volume for calculated weight based dose (refer to pharmacy reference sheets) is to be added to 40 ml of 0.9% Sodium Chloride (normal saline) USP prior to being administered to the patient as an infusion, at a flow rate of less than or equal to 2.5 ml/min over ~60 minutes.

During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Vials of BMS-986214 injection must be stored at 2° to 8°C (36° to 46°F) protected from light and it must not be frozen. Further instructions for dilution and infusion of BMS-986214 injection may be provided in the clinical protocol, 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 between BMS-986214 and polyvinyl chloride (PVC) and polyolefin containers/IV components have been observed.

4.5.1 Dose Delay Criteria

Regardless of whether or not the event is attributed to nivolumab, ipilimumab, or BMS-986214, all study drugs must be delayed until treatment can resume. Tumor assessments for all subjects should continue as per protocol even if dosing is delayed. During Part 1, both nivolumab and ipilimumab should be discontinued at the same time.

Nivolumab, ipilimumab, and BMS-986214 administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related adverse event, with the following exception:
  - Grade 2 drug-related fatigue does not require a treatment delay
  - Grade 2 drug-related creatinine, AST, ALT or Total Bilirubin abnormalities
- Any Grade 3 skin, drug-related adverse event
- Any Grade 3 drug-related laboratory abnormality (excluding AST, ALT or Total Bilirubin), with the following exceptions for lymphopenia, and asymptomatic amylase or lipase:
  - Grade 3 lymphopenia does not require dose delay
  - Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication

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

4.5.2 Criteria to Resume Treatment

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 TBILI 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 4.5.2) 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 with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor.

4.5.3 Dose Discontinuation

Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, or recurs with the following exceptions for laboratory abnormalities, diarrhea drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:

- Grade 3 drug-related diarrhea, uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
- Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
- Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
  - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
  - Any drug-related liver function test (LFT) abnormality that meets the following criteria require 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
  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 drug-related endocrinopathy adverse events, such as adrenal insufficiency, ACTH deficiency, 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
- 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.

4.5.4 Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD. [7]

Subjects treated with study drug(s) will be permitted to continue treatment beyond initial RECIST 1.1 defined PD in both Part 1 and Part 2, assessed by the investigator, 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 treatment. All other elements of the main consent including description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply

A radiographic assessment/ scan should be performed within 6 weeks of initial investigator-assessed progression to determine whether there has been a decrease in the tumor size or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment with nivolumab.

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.

For the subjects who continue 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 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 least 15 mm). Any new lesion considered non-measureable at the time of initial progression may 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.

4.5.5 Management Algorithms for Immuno-Oncology Agents

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab, ipilimumab, and BMS-986214 are considered immuno-oncology agents in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Management Algorithms have been developed to assist investigators in assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic

- Endocrinopathy
- Skin
- Neurological

The above algorithms are found in the Appendix 3 of this protocol.

4.5.6 Treatment of Related Infusion Reactions

Since study drug contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the study medical monitor and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (Version 4.0) guidelines.

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

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

- Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional nivolumab 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 study drug 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 study drug will be administered at that visit
- 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 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 study drug. 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. Study drug 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).

4.6 Blinding/Unblinding

Not applicable.

4.7 Treatment Compliance

Treatment compliance will be monitored by drug accountability as well as the subject's medical record and electronic case report form (eCRF).

4.8 Destruction or Return of Investigational Product

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

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

It is the investigator's or designee's responsibility to arrange for disposal, provided that procedures for proper disposal have been established according to applicable federal, state, local, and

institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The following minimal standards must be met:

- On-site disposal practices must not expose humans to risks from the drug
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period

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

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

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

4.9 Retained Samples for Bioavailability / Bioequivalence

At the time of receipt of the investigational product by the investigator or designee's, BMS will specify the appropriate number of containers or units to select for retention, the conditions of sample storage, required duration of sample retention, and provisions for returning or disposing of the investigational product. When samples are selected, containers or units should be placed in packaging with a tamper evident seal provided by BMS. Package labeling should clearly identify the contents as bioavailability/bioequivalence (BA/BE) samples and state that the investigational product should be stored in the restricted area with limited access.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Procedural Outline (CA209742)

Procedure	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	Prior to any screening procedures
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening and confirmed prior to randomization
Medical History	X	
Tumor Tissue Samples	X	Sufficient tumor tissue obtained in the metastatic setting or from an unresectable site (block or a minimum of 20 slides is requested with a minimum of 10 slides required, obtained from core biopsy, punch biopsy, excisional biopsy or surgical specimen) In order to be randomized, a subject must have quantifiable PD-L1 expression (≥ 5% or < 5% tumor cell membrane staining) or be classified as PD-L1 indeterminate
Safety Assessments		
Physical Examination	X	Careful assessment for hypersensitivity, anaphylaxis or any infusion related reactions
Vital Signs	X	Including BP, HR, performance status, and temperature. Obtain vital signs at the screening visit
Assessment of Signs and Symptoms	X	For screening, within 14 days prior to 1st dose
12-Lead Electrocardiogram (ECG)	X	For screening, within 14 days prior to 1st dose

Table 5.1-1: Screening Procedural Outline (CA209742)

Procedure	Screening Visit	Notes
Laboratory Tests	X	CBC with differential, Chemistry panel including LDH, AST, ALT, ALB, ALP, T Bili, BUN or serum urea level, creatinine, Ca, Na, K, Cl, Glucose, amylase, lipase, TSH, Free T4, Free T3, within 14 days of randomization; hepatitis B surface antigen (HBVsAg), and hepatitis C antibody (HCV Ab) or hepatitis C RNA (HCV RNA), within 28 days of randomization
Pregnancy Test (WOCBP only)	X	Serum or urine to be done at screening visit and repeated within 24 hours prior to first dose of study drug.
Clinical Drug Supplies		
Randomize	X	First dose to be administered within 3 working days following randomization.
Screening/Baseline Tumor Assessment	X	Chest, Abdomen, Pelvis, and Brain within 28 days prior to first dose. Head MRI is required in subjects with known history of brain metastases; subjects without known history of brain metastases may have head CT or MRI

Table 5.1-2: Short-term Procedural Outline (CA209742)

Procedure	For Part 1, Study Drug Every 3 Weeks for 4 Doses (Both Arm A and Arm B)	Notes
	Cycle 1, 2, 3, 4 (Day 1)	
Safety Assessments		
Targeted Physical Examination	X	To be performed only as clinically indicated within 72 hours prior to dosing
Vital Signs	X	Including BP, HR, and temperature.
Physical Measurements (including ECOG performance status)	X	Weight and ECOG Performance status within 72 hours prior to dosing
Adverse Events Assessment	Continuously	
Review of Concomitant Medications	X	
Laboratory Tests	X	Within 72 hrs prior to dosing to include CBC w/ differential, LFTs, BUN or serum urea level, creatinine, Ca, Na, K, Cl, LDH, Glucose, amylase, lipase, TSH (+ reflex Free T4 and Free T3)
Pregnancy Test (WOCBP only)	X	Serum or urine within 24 hours prior to administration of first dose and every 3 weeks thereafter in Part 1 of the study. A negative pregnancy test should be documented within 24 hours prior to start of each dose of investigational product.
Pharmacokinetic and Immunogenicity Assessments		
Immunogenicity blood sample	X	Refer to Table 5.5.1-1
PK Samples	X	Refer to Table 5.5.1-1
[redacted]		

Table 5.1-2: Short-term Procedural Outline (CA209742)

Procedure	For Part 1, Study Drug Every 3 Weeks for 4 Doses (Both Arm A and Arm B) Cycle 1, 2, 3, 4 (Day 1)	Notes
[redacted]ers	[redacted]	[redacted]
[redacted])	[redacted]	[redacted].
[redacted]	[redacted]	[redacted].
[redacted]	[redacted]	[redacted]
Efficacy Assessment		
Tumor Assessment	See Notes	FIRST tumor assessment should be performed at 12 weeks (± 1 wk) following randomization. CT Chest, CT (or MRI) abdomen, pelvis and all known sites of disease. Use same imaging method as was used at screening/baseline. Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated
Outcomes Research Assessments		
EORTC QLQ-C30 and EQ-5D (3-Level Version)	X	To be completed at the start of the clinic visit every 6 weeks. First questionnaire should be completed after IRT randomization but before dosing. (Cycle 1, 3)
Health Care Utilization	X	Health Care Utilization will be collected at each visit
Clinical Drug Supplies		
IRT Drug Vial Assignment	X	Within 24 hours prior to dosing
Administer Study Treatment	X	First dose to be administered within 3 working days following randomization.

Table 5.1-3: On-Study Assessments - Part 2 (CA209742)		
Procedure	**For Part 2, Study Drug is Administered Every 4 Weeks (Both Arm A and Arm B)** **Cycle 5 and beyond (Day 1)**	**Notes** **Cycle 5 will begin 6 weeks after Cycle 4 dose**
Safety Assessments		
Targeted Physical Examination	X	To be performed only if clinically indicated within 72 hours prior to dosing
Vital Signs	X	Including BP, HR, temperature
Physical Measurements (including ECOG performance status)	X	Weight and ECOG Performance status within 72 hours prior to dosing
Adverse Events Assessment	Continuously	
Review of Concomitant Medications	X	
Laboratory Tests	X	Beginning at Cycle 5 and every alternate dose thereafter (Cycle 7, 9, 11, 13, etc), on-study local laboratory assessments should be done within 72 hours prior to dosing and include: CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Na, K, Cl, LDH, glucose, amylase, lipase, TSH with reflexive Free T4, Free T3. Beginning at Cycle 6 and every alternate dose thereafter (Cycle 8, 10, 12, 14, etc), on-study local laboratory assessment should be done within 72 hours prior to dosing and include: LFTs (ALT, AST, total bilirubin, alkaline phosphatase) and creatinine.
Pregnancy Test (WOCBP only)	X	Serum or urine within 24 hours prior to first dose and every 4 weeks thereafter. A negative pregnancy test should be documented within 24 hours prior to start of each dose of investigational product.
Outcomes Research Assessments		
EORTC QLQ-C30 and EQ-5D-3L	X	To be completed at the start of the clinic visit every 4 weeks from Cycle 5 onwards
Health Care Utilization	X	Health Care Utilization will be collected at each visit from Cycle 5 onwards

Table 5.1-3: On-Study Assessments - Part 2 (CA209742)		
Procedure	**For Part 2, Study Drug is Administered Every 4 Weeks (Both Arm A and Arm B)** **Cycle 5 and beyond (Day 1)**	**Notes** **Cycle 5 will begin 6 weeks after Cycle 4 dose**
Pharmacokinetic and Immunogenicity Assessments		
Immunogenicity blood sample	X	
PK Samples	X	
Efficacy Assessment		
Tumor Assessment	See Notes	First tumor assessment during Part 2 should occur after 8 weeks (± 1wk) relative to previous tumor assessment performed at week 12. Subsequent tumor assessments should occur every 8 weeks (± 1 wk) for the first 12 months from randomization. From the second year from randomization, tumor assessments should occur every 12 wks (± 2 wk) until disease progression. CT Chest, CT (or MRI) abdomen, pelvis and all known sites of disease. Use same imaging method as was used at screening/baseline. Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated.
Clinical Drug Supplies		
IRT Drug Vial Assignment	X	
Administer Study Treatment	X	Note: Within 3 working days from vial assignment, the subject must receive the dose of study medication.

Table 5.1-4: Follow-up Assessments (CA209742)

Procedure	Follow Up,[a] Visits X1 and X2	Survival,[b] Follow-up Y Visits	Notes
Safety Assessments			
Targeted Physical Examination	X		To assess for potential late emergent study drug related issues
Adverse Event Assessments	X	X	
Laboratory Tests	X		On site/local CBC w/differential, LFTs, BUN or serum urea level, creatinine, amylase, lipase and TSH (+ reflex Free T4 and Free T3) for X1, repeat at X2 if study drug related toxicity persists.
Pregnancy Test (WOCBP Only)	X		Serum or urine
Review of Concomitant Medications	X		
Pharmacokinetic and Immunogenicity Assessments			
PK Samples	X		Refer to Table 5.5.1-1
Immunogenicity blood sample	X		Refer to Table 5.5.1-1
Survival Status			
Subject Status	X	X	Every 3 months, Survival Follow up Visits may be accomplished by visit or phone contact, to include subsequent anti-cancer therapy

Table 5.1-4: Follow-up Assessments (CA209742)			
Procedure	**Follow Up,[a] Visits X1 and X2**	**Survival,[b] Follow-up Y Visits**	**Notes**
Efficacy Assessments			
Tumor Assessments	See Notes		Only for subjects without progression on study therapy. FIRST tumor assessment should first be performed at 12 weeks (± 1 wk) following randomization SUBSEQUENT tumor assessments should occur every 8 weeks (± 1 wk) thereafter for the first 12 months, then every 12 wks (± 2 wk) until disease progression CT Chest, CT (or MRI) abdomen, pelvis and all known sites of disease. Use same imaging method as was used at screening/baseline. Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated
EORTC QLQ-C30	X		Follow-up visits 1 and 2 only
EQ-5D-3L	X	X	Follow-up visits 1 and 2 and every 3 months for the first 12 months then every 6 months thereafter for the survival follow-up visits.
Health Care Utilization	X		Follow-up visits 1 and 2 only
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]

[a] X visits occur as follows - X1 = 30 days from the last dose (± 7 days) or coincide with the date of discontinuation (± 7 days) if date of discontinuation is greater than 37 days after last dose, X2 = 84 days (± 7 days) from follow-up visit 1. Follow up visits X1 and X2 will occur only after patient completes all study treatment.

[b] Y Survival visits = every 3 months from X2 (± 7 days).

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 4.0
- BMS-936558 (nivolumab) IB
- Ipilimumab IB
- Fixed Ratio Combination (FRC) BMS-986214 IB
- Pharmacy Information Sheets
- Laboratory manuals for collection and handling of blood (including biomarker and immunogenicity) and tissue specimens
- Site manual for operation of IRT, including enrollment worksheets
- Manual for entry of local laboratory data
- Serious Adverse Events (or eSAE) case report form pages
- Pregnancy surveillance forms
- RECIST 1.1 pocket guide
- Quality of Life questionnaires: EORTC QLQ-C30 and EQ-5D-3L

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 randomization.

Screening local laboratory assessments should be done within 14 days prior to randomization 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.

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

The following screening local laboratory assessments should be done within 28 days prior to randomization: Hepatitis B and C testing (HBV sAg and HCV Ab or HCV RNA).

While on-study the following local laboratory assessments are to be done within 72 hours prior to each dose in Part 1: CBC with differential, LFTs, BUN or serum urea level, creatinine, Ca, Na, K, Cl, LDH, Glucose, amylase, lipase, and TSH (+ reflex Free T4 and Free T3)

While on-study the following local laboratory assessments are to be done within 72 hours prior to each dose in Part 2: Beginning at Cycle 5 and every alternate dose thereafter (Cycle 7, 9, 11, 13, etc), on-study local laboratory assessments should be done within 72 hours prior to dosing and include: CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Na, K, Cl, LDH, glucose, amylase, lipase, TSH with reflexive Free T4, Free T3. Beginning at Cycle 6 and every alternate dose thereafter (Cycle 8, 10, 12, 14, etc), on-study local laboratory assessment should be done within 72 hours prior to dosing and include: LFTs (ALT, AST, total bilirubin, alkaline phosphatase) and creatinine.

Thyroid function testing (TSH with reflexive fT3 and fT4) is to be done every 8 weeks for subjects receiving nivolumab at 480 mg q4w (every other infusion).

On treatment pregnancy tests should be performed as per the schedule in the Time and Events table.

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/email correspondence to assess the subject's status are acceptable.

Adverse events and laboratory values will be graded according to the NCI-CTCAE version 4.0.

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.

On treatment local laboratory assessments are to be completed within 3 working days prior to dosing.

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 Appendix 3.

Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or

assessments may be performed as clinically necessary or where required by institutional or local regulations.

5.3.1 Imaging Assessment for the Study

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

5.4 Efficacy Assessments

Study evaluations will take place in accordance with the flow charts in Section 5.1. Baseline assessments should be performed within 28 days prior to randomization utilizing CT or MRI. In addition to chest, abdomen, pelvis, and brain, all known sites of disease should be assessed at baseline. Subsequent assessments should include chest, abdomen, and pelvis, and all known sites of disease and should use the same imaging method as was used at baseline. Subjects will be evaluated for tumor response beginning 12 weeks (± 1 week) from randomization and continuing every 8 weeks (± 1 week) for the first 12 months and every 12 weeks (± 1 week) thereafter, until disease progression is documented or treatment is discontinued (whichever occurs later). Tumor assessments for ongoing study treatment decisions will be completed by the investigator using RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 criteria.

5.4.1 Primary Efficacy Assessment

Efficacy assessment is not a primary endpoint. The primary endpoint is the incidence of AEs in the Broad Scope MedDRA Anaphylactic Reaction SMQ occurring within 2 days after dosing during the combination, Part 1 period. See Section 6 for a further description of adverse event reporting.

5.4.2 Secondary Efficacy Assessments

The secondary measure of efficacy will include the ORR and PFS.

The ORR, will be determined by the investigator using RECIST 1.1 criteria, in all treated subjects. ORR is defined as the number of subjects with a BOR of complete response (CR) or partial response (PR) divided by the number of treated subjects. The investigator-determined ORR will be further characterized by the investigator-determined duration of response (DOR) and the magnitude of reduction in tumor volume

The other secondary efficacy measure will be to evaluate PFS in all treated patients.

5.4.2.1 Measurable Lesions

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

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

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

5.4.2.2 Non-measurable Lesions

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions.

- Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, 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.

5.4.2.3 Special Considerations Regarding Lesion Measurability

Bone Lesions

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

Cystic Lesions

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are by definition, simple cysts.

"Cystic lesions" thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same subject, these are preferred for selection as target lesions.

Non-measurable Lesions

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

5.4.3 Specifications for Method of Measurement

5.4.3.1 Measurement of Lesions

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

5.4.3.2 Method of Assessment

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

5.4.3.3 CT/MRI Scan

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

5.4.3.4 Chest X-Ray

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

5.4.3.5 Clinical Lesions

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

5.4.3.6 Ultrasound

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

5.4.3.7 Endoscopy, Laparoscopy

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

5.4.3.8 Tumor Markers

Tumor markers such as, but not limited to, LDH may be used for clinical management, but will not be included in the assessment of BOR.

5.4.4 Baseline Documentation of "Target" and "Non-Target Lesions"

5.4.4.1 Target Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

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

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted below, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Previously treated CNS metastases are not considered measurable lesions for purposes of RECIST 1.1 determined response.

5.4.4.2 Lymph Nodes

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum.

Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

5.4.4.3 Non-target Lesions

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". In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (eg, "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

5.4.5 Tumor Evaluation

Evaluation of Target Lesions

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

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

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on

study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

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

5.4.5.1 Target Lesions that Become "Too Small to Measure"

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

5.4.5.2 Target Lesions that Split or Coalesce on Treatment

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

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

5.4.5.3 Evaluation of Non-target Lesions

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

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

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

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

5.4.5.4 Unequivocal Progression in Non-target Disease

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

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

5.4.5.5 New Lesions

The appearance of new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions. This is particularly important

when the subject's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan reported as a "new" cystic lesion, which it is not.

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

5.4.6 Response Criteria (RECIST 1.1)

For subjects who have measurable disease at baseline, Table 5.4.6-1 provides a summary of the overall response status calculation at each time point.

Table 5.4.6-1: Time Point Response - Subjects with Target (± Non-target) Disease

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

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

5.4.6.1 Missing Assessments and Not Evaluable Designation

When no imaging/measurement is done at all at a particular time point, the subject is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not have changed the assigned time-point response.

5.4.6.2 Confirmation of Scan

Verification of Response: As per RECIST 1.1, confirmation of response is required for trials with response as a primary endpoint but is no longer required in randomized studies since the control arm serves as appropriate means of interpretation of data. Hence, confirmation is NOT required.[34]

Verification of Progression: Progression of disease should be verified in cases where progression is equivocal. If repeat scans confirm PD, then progression should be declared using the date of the

initial scan. If repeat scans do not confirm PD, then the subject is considered not to have progressive disease per RECIST 1.1.

5.4.6.3 Best Overall Response

The BOR is determined once all the data for the subject is known. It is defined as the best response designation, as determined by the investigator, recorded between the date of randomization and the date of objectively documented progression per RECIST1.1 or the date of subsequent therapy, whichever occurs first. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR assessment. The subject's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

For the purpose of this study, the scan time from baseline for determination of SD will be 12 weeks (± 1 week); therefore, a minimum of 11 weeks.

5.4.6.4 Duration of Objective Response

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

5.5 Pharmacokinetic Assessments

Samples for PK and immunogenicity assessments will be collected for all subjects receiving nivolumab and ipilimumab as described in Table 5.5.1-1. All time points are relative to the start of study drug administration. All on-treatment time points are intended to align with days on which study drug is administered. If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected but the dose is subsequently delayed, an additional predose sample should not be collected. Further details of sample collection, processing, and shipment will be provided in the laboratory procedures manual.

Blood samples should be drawn from a site other than the infusion site (ie, contralateral arm) on days of infusion. All samples collected pre-dose should be taken just prior to the administration from the contralateral arm (ie, the arm not used for the infusion). If the infusion was interrupted, the interruption details will also be documented on the CRF. Blood samples will be processed to collect serum and stored preferably at -70°C (samples may be stored at -20°C up to 2 months). Further details of pharmacokinetic sample collection and processing will be provided to the site in the lab manual.

5.5.1 Pharmacokinetic and Immunogenicity Sample Analyses

Serum samples will be analyzed for drug (nivolumab and ipilimumab) and ADA (anti-nivolumab and anti- ipilimumab antibodies) by validated immunoassays. Samples with a positive ADA response may also be analyzed for neutralizing ADA response to nivolumab and/or ipilimumab.

[redacted]

Table 5.5.1-1: Pharmacokinetic and Immunogenicity Sample Collections (CA209742-Arms A and B)

Part[a]	Study Day[b] (1 Cycle = 3 weeks for Part 1 1 Cycle = 4 Weeks for Part 2)	Time (Event)	Time (Relative to Start of Infusion) Hours:Min	Pharmacokinetic Blood Sample for Nivolumab	Immunogenicity Blood Sample for Nivolumab	Pharmacokinetic Blood Sample for Ipilimumab	Immunogenic Blood Sample for Ipilimumab
1	C1D1	(Predose)[c]	00:00	X	X	X	X
1	C1D1	(EOI-nivo)[d]	00:60	X			
1	C1D1	(EOI-ipi)[d]	00:60 or 00:90			X	
1	C2D1	(Predose)[c]	00:00	X	X	X	X
1	C2D1	(EOI-nivo)[d]	00:60	X			
1	C2D1	(EOI-ipi)[d]	00:60 or 00:90			X	
1	C4D1	(Predose)[c]	00:00	X	X	X	X
1	C4D1	(EOI-nivo)[d]	00:60	X			
1	C4D1	(EOI-ipi)[d]	00:60 or 00:90			X	
2	C5D1	(predose)c	00:00	X	X	X	X
2	CXD1: Every 16 weeks starting with C5D1 (ie, C9D1, C13D1, etc.)	(Predose)	00:00	X	X		
	First 2 Follow-up Visits (Approximately 30 days and up to ~ 100 Days from the Discontinuation of Study Drug)	NA		X	X		

[a] Part 1 indicates first 12 weeks (or 4 cycles) of combination treatment (nivolumab + ipilimumab). Part 2 indicates nivolumab monotherapy period starting from Week 16 (or Cycle 5).

[b] If a subject discontinues study drug treatment during the sampling period, they will move to sampling at the follow-up visits.

[c] Predose: All predose samples for nivolumab and ipilimumab should be taken prior to the start of nivolumab or FRC infusion.

[d] EOI-nivo and EOI-ipi PK samples: End of Infusion PK samples for nivolumab and ipilimumab, respectively. **For sequential dosing, EOI samples for nivolumab and ipilimumab should be collected immediately (preferably within 2 - 5 minutes) prior to the end of the 60 minute nivolumab infusion and 90 minutes ipilimumab infusion, respectively. For the FRC dosing, EOI samples for nivolumab and ipilimumab should be collected immediately (preferably within 2 - 5 minutes) prior to the end of the 60 min FRC co-infusion.** If the end of any infusion is delayed, the collection of the EOI samples should be delayed accordingly.

5.7 Outcomes Research Assessments

- European Organization for Research and Treatment of Cancer QLQ-C30[35]

It is a 30-item instrument that has gained wide acceptance in oncology clinical studies. The EORTC QLQ-C30 is composed of multi-item and single-item scales. The global health status/QoL scale is composed of two items. In addition to the global health status/QoL scale, the EORTC QLQ-C30 includes five functional scales (physical, role, emotional, social, and cognitive), three symptom scales (fatigue, nausea and vomiting, and pain), and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The overall health status/QoL responses are seven-point Likert scales ranging from 1 (Very Poor) to 7 (Excellent), while the responses for all functional and symptom items are four-point categorical scales ranging from 1 (Not at all) to 4 (Very much). Scale items are scored using recommended EORTC procedures[36]. Raw scores are transformed to a linear scale ranging from 0 to 100, with a higher score representing a higher global health status/QoL. The reliability and validity of the questionnaire is highly consistent across different language-cultural groups.

- The 3-level EQ-5D:[37]

The EQ-5D is a standardized instrument used to measure self-reports of health status and functioning. The instrument's descriptive system consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels, reflecting "no health problems," "moderate health problems," and "extreme health problems." A dimension for which there are no problems is said to be at level 1, while a dimension for which there are extreme problems is said to be at level 3. Thus, the vectors 11111 and 33333 represent the best health state and the worst health state, respectively, described by the EQ-5D. Altogether, the instrument describes $3^5 = 243$ health states. Empirically derived weights can be applied to an individual's responses to the EQ-5D descriptive system to generate an index measuring the value to society of his or her current health. Such preference-weighting systems have been developed for Japan, UK, US, Spain, Germany, and numerous other populations. In addition, the EQ-5D includes a visual analog scale (VAS) that allows respondents to rate their own current health on a 100-point scale ranging from "best imaginable" to "worst imaginable" health.

Subjects will be asked to complete the EORTC QLQ-C30 and the EQ-5D-3L before any clinical activities are performed during on-study clinic visits and at designated visits during the follow-up and survival phases. Questionnaires will be provided in the subject's preferred language, if available.

5.8 Other Assessments

Not applicable.

5.9 Additional Research Collection

Additional research collections are mandatory for all participants, except where prohibited by local laws or regulations, ethics committees or where a waiver is provided by the BMS Study Director. Where one or more of these exceptions occurs, participation in the additional research collection should be encouraged but will not be a condition of overall study participation, and subjects may

opt out of the collection. This protocol will include residual sample storage for additional research (AR).

This collection for additional research is intended to expand the translational R&D capability at Bristol-Myers Squibb, and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. It may also be used to support health authority requests for analysis, and advancement of pharmacodiagnostic development to better target drugs to the right patients. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression and response to treatment etc.

All requests for access to samples or data for additional research will be vetted through a diverse committee of the study sponsor's senior leaders in Research and Development to ensure the research supports appropriate and well-defined scientific research activities.

- Additionally, residual blood and tissue collections will also be retained by the BMS Biorepository in Hopewell, NJ or at a BMS approved third party storage management facility for additional research purposes
- Additional research samples will be retained for 15 years or the maximum allowed by applicable law. No additional sampling is required for residual collections

Further details of sample collection and processing will be provided to the site in the procedure manual.

[redacted]

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

[redacted]

[redacted]

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 nivolumab. For subjects randomized/assigned to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of randomization. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

The investigator must report any SAE that occurs after these time periods and that is believed to be related to 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).

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

All nonserious adverse events (not only those deemed to be treatment-related) 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.

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form electronic) as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

- Any laboratory test result that is clinically significant or meets the definition of an SAE

- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy

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

6.4 Pregnancy

If, following initiation of the 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.

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.

6.5 Overdose

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

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

6.6 Potential Drug Induced Liver Injury (DILI)

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

Potential drug induced liver injury is defined as:

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

6.7 Other Safety Considerations

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

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

Not applicable.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

Approximately 102 subjects will be randomized to the 2 treatment arms in a 1:1 ratio in order to target 100 treated subjects (50 per arm). This number of treated subjects was chosen to achieve a sufficient level of precision for a descriptive analysis to estimate the difference in rates of AEs in the Broad Scope MedDRA Anaphylactic Reaction SMQ between the two treatment arms. Fifty treated subjects per arm will allow estimation of the rate difference within 95% confidence limits of +/- 20% or less and will be supplemented by a qualitative clinical assessment of the type and severity of events to evaluate benefit-risk.

In previously submitted Phase 2/3 studies of nivolumab in combination with ipilimumab (CA209069 and CA209067), AEs in the MedDRA Anaphylactic Reaction SMQ (broad scope) with onset within 2 days after sequential dosing of nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg were reported in 24% of treated subjects. In the current study, if the observed rate of these events is equal to 24% among 50 treated subjects in each arm, then the 95% CI for the difference in rates between arms will be (-16.7%, 16.7%).

Table 8.1-1 shows the precision that the sample size of 50 treated subjects per arm will provide for estimating rates and rate differences between the treatment arms under different assumed observed rates.

Table 8.1-1: 95% CI for Rates and Rate Differences when Observed in 50 Subjects per Arm

Observed AE Rate (95% CI)		Observed Rate Difference (95% CI)
Arm A (Co-administration, FRC)	Arm B (Sequential administration)	Arm A - Arm B
24% (13.1%, 38.2%)	22% (11.5%, 36.0%)	2% (-14.5%, 18.5%)
24% (13.1%, 38.2%)	24% (13.1%, 38.2%)	0% (-16.7%, 16.7%)
26% (14.6%, 40.3%)	24% (13.1%, 38.2%)	2% (-15.0%, 19.0%)
30% (17.9%, 44.6%)	28% (16.2%, 42.5%)	2% (-15.8%, 19.8%)
30% (17.9%, 44.6%)	30% (17.9%, 44.6%)	0% (-18.0%, 18.0%)

8.2 Populations for Analyses

The first (primary) analysis will be carried out for the primary endpoint and safety- and PK-related secondary endpoints when all subjects who are still on-treatment have completed the Part 1 period. The final analysis will be carried out for the efficacy-related secondary endpoints and, if data are available, the exploratory endpoints when all subjects have had at least 9 months of follow-up.

Since the primary objective will be addressed by a safety endpoint, the primary endpoint analysis will be based on all treated subjects. For consistency, the secondary endpoints will use the same analysis population as the primary endpoint (ie, all treated subjects).

- All Enrolled Subjects: All subjects who signed an informed consent form and were registered into the IRT.
- All Randomized Subjects: All subjects who were randomized to any treatment group. This is the primary dataset for efficacy listings.
- All Treated Subjects: All subjects who received at least one dose of any study medication. This is the primary dataset for analysis of study conduct, study population, efficacy (including secondary endpoints), exposure, and safety (including primary endpoint).
- PK Subjects: All treated subjects with available serum time-concentration data.
- Immunogenicity Subjects: All treated subjects with available ADA data.
- Biomarker Subjects: All treated subjects with available biomarker data.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

The primary endpoint of the study is the incidence of AEs in the Broad Scope MedDRA Anaphylactic Reaction SMQ occurring within 2 days after dosing during the combination, Part 1 period. This incidence rate is defined as number of subjects who experienced at least 1 AE in the MedDRA Anaphylactic Reaction broad scope SMQ with onset on the day of or within 2 days after any study therapy infusion during the combination period (Part 1) divided by number of treated

subjects. For reference, the terms currently included in the MedDRA Anaphylactic Reaction SMQ based on MedDRA version 19.0 are listed in Table 8.3.1-1.

The analysis of the primary endpoint will occur at the time of first (primary) analysis when all subjects who are still on-treatment have completed the Part 1 period.

Table 8.3.1-1: Preferred Terms Included in the MedDRA Anaphylactic Reaction SMQ - Broad and Narrow Scopes

Preferred Term[a]	Term Scope[b]
Acute respiratory failure	Broad
Allergic oedema	Broad
Anaphylactic reaction	Narrow
Anaphylactic shock	Narrow
Anaphylactic transfusion reaction	Narrow
Anaphylactoid reaction	Narrow
Anaphylactoid shock	Narrow
Angioedema	Broad
Asthma	Broad
Blood pressure decreased	Broad
Blood pressure diastolic decreased	Broad
Blood pressure systolic decreased	Broad
Bronchial oedema	Broad
Bronchospasm	Broad
Cardiac arrest	Broad
Cardio-respiratory arrest	Broad
Cardio-respiratory distress	Broad
Cardiovascular insufficiency	Broad
Chest discomfort	Broad
Choking	Broad
Choking sensation	Broad
Circulatory collapse	Narrow
Circumoral oedema	Broad
Cough	Broad
Cyanosis	Broad
Dialysis membrane reaction	Narrow
Diastolic hypotension	Broad
Dyspnoea	Broad
Erythema	Broad
Eye oedema	Broad
Eye pruritus	Broad
Eye swelling	Broad
Eyelid oedema	Broad
Face oedema	Broad
Flushing	Broad

Table 8.3.1-1: Preferred Terms Included in the MedDRA Anaphylactic Reaction SMQ - Broad and Narrow Scopes

Preferred Term[a]	Term Scope[b]
Generalised erythema	Broad
Hyperventilation	Broad
Hypotension	Broad
Injection site urticaria	Broad
Irregular breathing	Broad
Kounis syndrome	Narrow
Laryngeal dyspnoea	Broad
Laryngeal oedema	Broad
Laryngospasm	Broad
Laryngotracheal oedema	Broad
Lip oedema	Broad
Lip swelling	Broad
Mouth swelling	Broad
Nasal obstruction	Broad
Nodular rash	Broad
Ocular hyperaemia	Broad
Oedema	Broad
Oedema mouth	Broad
Oropharyngeal spasm	Broad
Oropharyngeal swelling	Broad
Periorbital oedema	Broad
Pruritus	Broad
Pruritus allergic	Broad
Pruritus generalised	Broad
Rash	Broad
Rash erythematous	Broad
Rash generalised	Broad
Rash pruritic	Broad
Respiratory arrest	Broad
Respiratory distress	Broad
Respiratory failure	Broad
Reversible airways obstruction	Broad
Sensation of foreign body	Broad
Shock	Narrow
Shock symptom	Narrow

Table 8.3.1-1: Preferred Terms Included in the MedDRA Anaphylactic Reaction SMQ - Broad and Narrow Scopes

Preferred Term[a]	Term Scope[b]
Skin swelling	Broad
Sneezing	Broad
Stridor	Broad
Swelling	Broad
Swelling face	Broad
Swollen tongue	Broad
Tachypnoea	Broad
Throat tightness	Broad
Tongue oedema	Broad
Tracheal obstruction	Broad
Tracheal oedema	Broad
Type I hypersensitivity	Narrow
Upper airway obstruction	Broad
Urticaria	Broad
Urticaria papular	Broad
Wheezing	Broad

[a] Changes may be made to this list with each new version of MedDRA. For information, the preferred terms defined at the time of finalization of this document are listed using MedDRA version 19.0.

[b] All Narrow Scope PTs are also included in the Broad Scope.

8.3.2 Secondary Endpoint(s)

The first secondary endpoint is the incidence of AEs in the MedDRA Anaphylactic Reaction narrow scope SMQ occurring within 2 days after any study therapy infusion during the combination period (Part 1). This incidence rate will be defined similarly to the primary endpoint except that the event rate will be based on terms within the narrow scope SMQ rather than the broad scope.

The second secondary endpoint is the incidence of events within the hypersensitivity/infusion reaction select AE category occurring within 2 days after any study therapy infusion during the combination period (Part 1). The select AEs consist of a list of preferred terms defined by the Sponsor and represent AEs with a potential immune-mediated etiology. At the time of this writing the following 5 MedDRA preferred terms are included in the hypersensitivity/infusion reaction select AE category: Anaphylactic Reaction, Anaphylactic Shock, Bronchospasm, Hypersensitivity, and Infusion Related Reaction. Changes may be made to this list with each new version of MedDRA prior to database lock. The list that is the most current at the time of analysis will be used. The incidence rate of hypersensitivity/infusion reaction select AEs will be defined

similarly to the primary endpoint except that the event rate will be based on terms from the hypersensitivity/infusion reaction select AE category rather than the MedDRA Anaphylactic Reaction broad scope SMQ.

The third secondary endpoint is the drug-related Grade 3 - 5 AE incidence rate defined using NCI CTCAE version 4.0 criteria. The drug-related Grade 3 - 5 AE rate is defined as number of subjects who experienced at least 1 AE of Grade 3 or higher, judged to be related to study drug by the investigator, and with onset on or after the first dose of study treatment and within 30 days of the last dose of study treatment, divided by number of treated subjects.

The fourth secondary endpoint is the all causality Grade 3 - 5 AE incidence rate defined using NCI CTCAE version 4.0 criteria. The all causality Grade 3 - 5 AE rate is defined as number of subjects who experienced at least 1 AE of Grade 3 or higher with onset on or after the first dose of study treatment and within 30 days of the last dose of study treatment, divided by number of treated subjects.

The fifth secondary endpoint is PK comparisons of nivolumab and ipilimumab administered as FRC to that of sequentially administered nivolumab and ipilimumab. PK will be measured using serum concentration-time data.

The sixth secondary endpoint is ORR as determined by investigators. The ORR is defined as the number of subjects with a BOR of CR or PR divided by the number of treated subjects for each treatment group. The BOR is defined as the best response designation, as determined by the investigator, recorded between the date of randomization and the date of objectively documented progression per RECIST 1.1 or the date of subsequent anti-cancer therapy, whichever occurs first. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR assessment. Tumor assessments are scheduled to be performed at Week 12 following randomization, every 8 weeks for the first 12 months and then every 12 weeks until disease progression.

The seventh secondary endpoint is PFS. PFS is defined as the time between the date of randomization and the first date of documented progression, as determined by the investigator, or death due to any cause, whichever occurs first. Subjects who die without a reported 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 their date of randomization. Subjects who started anti-cancer therapy without a prior reported progression will be censored on the date of their last evaluable tumor assessment prior to the initiation of subsequent anti-cancer therapy.

Safety- and PK-related secondary endpoints will be analyzed at the time of the first (primary) analysis when all subjects who are still on-treatment have completed the Part 1 period. Efficacy-related secondary endpoints will be analyzed at the time final analysis when all subjects have had at least 9 months of follow-up.

[redacted]

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized in all treated subjects by treatment group, as treated, using descriptive statistics.

8.4.2 Efficacy Analyses

The primary endpoint is related to safety and there are no primary efficacy endpoints. Analysis methods for the primary safety endpoint are described in Section 8.4.3.1.

8.4.2.1 Secondary Endpoint Methods

Descriptive analyses of secondary efficacy endpoints will be performed.

ORRs and corresponding 95% exact CIs will be calculated using the Clopper Pearson method for each of the treatment arms. BOR will be tabulated for each treatment group. Associated odds ratios and 95% CIs for Arm A relative to Arm B will be calculated using Cochran-Mantel-Haenszel (CMH) methodology, adjusting for the stratification factors PD-L1 expression and M stage at

screening. An estimate of the difference in ORRs and corresponding 2-sided 95% CI will be calculated using CMH methodology, adjusting for the same stratification factors as above.

PFS curves for each treatment group will be estimated using the Kaplan-Meier (KM) product limit method. Median PFS and corresponding two-sided, 95% confidence intervals will be computed. Descriptive HRs and corresponding two sided 95% CIs for Arm A relative to Arm B will be estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by PD-L1 status and M Stage at screening. PFS rates at 6 months with 95% CIs will be estimated using KM methodology.

[redacted]

8.4.3 Safety Analyses

8.4.3.1 Primary Endpoint Methods

For the primary analysis, the incidence of AEs in the Broad Scope MedDRA Anaphylactic Reaction SMQ occurring within 2 days after any dose in Part 1 dosing by treatment arm, the difference in rates between arms, and the corresponding 95% confidence intervals will be reported descriptively. The confidence intervals for the rate estimates will be based on the Clopper and Pearson method. The estimate and confidence interval for the rate difference will be based on CMH method of weighting, adjusting for PD-L1 status and M Stage at screening. Descriptive statistics will be presented using NCI CTCAE version 4.0 by treatment group. Events will be tabulated using worst grade per NCI CTCAE v 4.0 criteria by preferred term.

8.4.3.2 Secondary Endpoint Methods

Anaphylactic reactions based on MedDRA narrow scope SMQ and hypersensitivity/infusion reaction select AEs will be summarized using the same methods as described above for the primary endpoint analysis. On-treatment drug-related Grade 3 - 5 AEs occurring within 30 days after the last dose of study treatment will be tabulated using worst grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term by treatment arm. All causality Grade 3-5 AEs will be summarized using similar methods as described for drug-related Grade 3-5 AEs.

8.4.3.3 Other Safety Analyses

Safety analyses will be performed in all treated subjects. Descriptive statistics of safety will be presented using NCI CTCAE v4.0 by treatment group. All on-study AEs, drug-related AEs, AEs

leading to discontinuation, 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 and changes from baseline including hematology, chemistry, liver function, and renal function will be summarized using worst grade NCI CTCAE v 4.0 criteria. Besides the secondary endpoint summaries of select AEs in the hypersensitivity/infusion reaction category, summaries and characterization of AEs of special clinical interest in other select categories will also be presented.

[redacted]

[redacted]

8.4.7 Other Analyses

Methodology for other analyses including immunogenicity and healthcare resource utilization is described in the statistical analysis plan.

8.5 Interim Analyses

Not Applicable.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if applicable, also by local health authority) except where necessary to eliminate an immediate hazard(s) to study subjects. If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining relevant approval/favorable opinion(s), the deviation or change will be submitted as soon as possible to:

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

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

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

9.1.2 Monitoring

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

If...	Then...
Supplied by BMS (or its vendors):	• amount received and placed in storage area

If...	Then...
	• amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each subject, including unique subject identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (eg, lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study drug integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy. These records should include: • label identification number or batch number • amount dispensed to and returned by each subject, including unique subject identifiers • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

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

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the 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)

For this single site protocol, the Principal Investigator for the site will sign the clinical study report.

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

11 LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
ACLS	advanced cardiac life support
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
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
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
A-V	atrioventricular
β-HCG	beta-human chorionic gonadotrophin
BA/BE	bioavailability/bioequivalence
%BE	percent biliary excretion
BID, bid	bis in die, twice daily
BLQ	below limit of quantification
BMI	body mass index
BMS	Bristol-Myers Squibb
BP	blood pressure
BRt	Total amount recovered in bile

Term	Definition
%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
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
CLD	Dialysate clearance of drug from plasma/serum
CLNR	nonrenal clearance
CLR	renal clearance
CLT	total body clearance
CLT/F (or CLT)	apparent total body clearance
CLT/F/fu or CLT/fu	Apparent clearance of free drug or clearance of free if (if IV)
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

Term	Definition
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)
ESR	Expedited Safety Report
F	bioavailability
Fb	fraction of bound drug
FDA	Food and Drug Administration
FI	fluctuation Index ([Cmax-Ctau)/Cavg])
FRC	fixed ratio combination
FRt	total amount recovered in feces
%FRt	total percent of administered dose recovered in feces
FSH	follicle stimulating hormone
%FE	percent fecal excretion
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

Term	Definition
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
K3EDTA	potassium ethylenediaminetetraacetic acid
K+	potassium
kg	kilogram
λz	terminal disposition rate constant
L	liter
LAM	Lactation amenorrhea method
LC	liquid chromatography
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

Term	Definition
mg	milligram
Mg++	magnesium
MIC	minimum inhibitory concentration
min	minute
mL	milliliter
mmHg	millimeters of mercury
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
MS	mass spectrometry
MTD	maximum tolerated dose
µg	microgram
N	number of subjects or observations
Na+	sodium
N/A	not applicable
ng	nanogram
NIMP	non-investigational medicinal products
NSAID	nonsteroidal anti-inflammatory drug
pAUCe	Extrapolated partial AUC from last quantifiable concentration to infinity
Pb	percent of bound drug
PD	pharmacodynamics
PK	pharmacokinetics
PO	per os (by mouth route of administration)
PT	prothrombin time
PTT	partial thromboplastin time

Term	Definition
Pu	percent of unbound drug
QC	quality control
QD, qd	quaque die, once daily
R2	coefficient of determination
RBC	red blood cell
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)
TID, tid	ter in die, three times a day
Tmax, TMAX	time of maximum observed concentration
TR_AUC(0-T)	AUC(0-T) treatment ratio
TR_AUC(INF)	AUC(INF) treatment ratio
TR_Cmax	Cmax treatment ratio
UR	urinary recovery
%UR	percent urinary recovery
URt	total amount recovered in urine
%URt	total percent of administered dose recovered in urine
UV	ultraviolet
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

Term	Definition
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
x g	times gravity

APPENDIX 1 ADDITIONAL ETHICAL CONSIDERATIONS

1 INFORMED CONSENT PROCEDURES

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

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records. Prior to the beginning of the study, the investigator must have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects.

The investigator must provide the subject, or, in those situations where consent cannot be given by subjects, their legally acceptable representative with a copy of the consent form and written information about the study in the language in which the subject is most proficient. The language must be non-technical and easily understood. The investigator should allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study, then informed consent must be signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion. The subject or legally acceptable representative should receive a copy of the signed informed consent and any other written information provided to study subjects prior to subject's participation in the study.

1.1 Subjects Unable to Give Written Informed Consent

1.1.1 Minors

For minors, according to local legislation, one or both parents or a legally acceptable representative must be informed of the study procedures and must sign the informed consent form approved for the study prior to clinical study participation. (In the event that the parents or legal guardians are unable to read, then an impartial witness should be present during the entire informed consent discussion). Whenever feasible, minors who are judged to be of an age of reason must also give their written assent by signing and dating the completed informed consent. All local laws, rules and regulations regarding informed consent of minors must be followed.

1.1.2 Subjects Experiencing Acute Events or Emergencies

A legally acceptable representative or legal guardian must provide informed consent when consent of the subject is not possible prior to clinical study participation, eg, for subjects experiencing an acute medical event such as myocardial infarction or stroke. Informed consent of the subject must additionally be obtained if they become capable of making and communicating their informed consent during the clinical study. All local laws, rules and regulations regarding informed consent of adult subjects incapable of giving informed consent must be followed.

1.1.3 Mentally Impaired or Incapacitated Subjects

Investigators (or whoever required by local regulations) should determine whether or not a mentally impaired or incapacitated subject is capable of giving informed consent and should sign a statement to that effect. If the subject is deemed mentally competent to give informed consent, the investigator should follow standard procedures. If the subject is deemed not to be mentally competent to give informed consent, a fully informed legal guardian or legally acceptable representative can be asked to give consent for, or on behalf of, the subject. All local laws, rules and regulations regarding informed consent of mentally impaired or incapacitated subjects must be followed.

Patients who are involuntarily hospitalized because of mental illness must not be enrolled in clinical studies

1.1.4 Other Circumstances

Subjects who are imprisoned or involuntarily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness must not be enrolled in clinical studies.

In circumstances where a subject's only access to treatment is through enrollment in a clinical study, eg, for subjects in developing countries with limited resources or for subjects with no marketed treatment options, the investigator must take special care to explain the potential risks and benefits associated with the study and ensure that the subject is giving informed consent.

When a subject may be in a dependent relationship with the investigator, a well-informed physician who is not engaged in the clinical study and is completely independent of the relationship between the subject and investigator should obtain the subject's informed consent.

1.1.5 Illiterate Subjects

If the subject, or, in those situations where consent cannot be given by the subject, their legally acceptable representative is unable to read, a reliable and independent witness should be present during the entire informed consent discussion. The choice of the witness must not breach the subject's rights to confidentiality. A reliable independent witness is defined as one not affiliated with the institution or engaged in the investigation. A family member or acquaintance is an appropriate independent witness. After the subject or legally acceptable representative orally consents and has signed, if capable, the witness should sign and personally date the consent form attesting that the information is accurate and that the subject, or, in those situations where consent cannot be given by subjects, their legally acceptable representative has fully understood the content of the informed consent agreement and is giving true informed consent.

1.2 Update of Informed Consent

The informed consent and any other information provided to subjects, or, in those situations where consent cannot be given by subjects, the subject's legally acceptable representative, should be revised whenever important new information becomes available that is relevant to the subject's consent, and should receive IRB/IEC approval/favorable opinion prior to use. The investigator, or a person designated by the investigator should fully inform the subject or the

subject's legally acceptable representative 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.

During a subject's participation in the study, any updates to the consent form and any updates to the written information will be provided to the subject.

APPENDIX 2 PERFORMANCE STATUS SCALES

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

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

APPENDIX 5 METHODS OF CONTRACEPTION

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

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. WOCBP and female partners of male subjects, who are WOCBP, are expected to use one of the highly effective methods of contraception listed below. Male subjects must inform their female partners who are WOCBP of the contraceptive requirements of the protocol and are expected to adhere to using contraception with their partner. Contraception methods are as follows:

1. Progestogen only hormonal contraception associated with inhibition of ovulation.
2. Hormonal methods of contraception including oral contraceptive pills containing combined estrogen + progesterone, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena®
3. Nonhormonal IUDs, such as ParaGard®
4. Bilateral tubal occlusion
5. Vasectomised partner with documented azoospermia 90 days after procedure
   a) Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success
6. Intrauterine hormone-releasing system (IUS)
7. Complete abstinence
   a) Complete abstinence is defined as the complete avoidance of heterosexual intercourse. (refer to Glossary of Terms)
   b) Complete abstinence is an acceptable form of contraception for all study drugs and must be used throughout the duration of the study treatment (plus 5 half-lives of the investigational drug plus 30 days)
   c) It is not necessary to use any other method of contraception when complete abstinence is elected
   d) Subjects who choose complete abstinence must continue to have pregnancy tests
   e) Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence
   f) The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject

UNACCEPTABLE METHODS OF CONTRACEPTION

1. Periodic abstinence (calendar, symptothermal, post-ovulation methods)
2. Withdrawal (coitus interruptus)

3. Spermicide only
4. Lactation amenorrhea method (LAM)