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Clinical Protocol CA209038

An Exploratory Study of the Biologic Effects of Nivolumab and Nivolumab in Combination with Ipilimumab Treatment in Subjects with Advanced Melanoma (Unresectable or Metastatic)

Revised Protocol 07
Incorporates Administrative Letter 01, 02, 04, & 05,
Amendment 02, 03, 04, 05, 06, 07, and 08

Study Director

[redacted]

Medical Monitor
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[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.

SYNOPSIS

Title of Study: An Exploratory Study of the Biologic Effects of Nivolumab and Nivolumab in Combination with Ipilimumab Treatment in Subjects with Advanced Melanoma (Unresectable or Metastatic)

Investigational Product: Nivolumab (also known as BMS-936558 or Anti-PD-1) and ipilimumab (BMS-724016).

Dose and Mode of Administration: Nivolumab will be administered as an intravenous (IV) infusion at the assigned dose and schedule. Ipilimumab will be administered at the dose of 3mg/kg. Treatment will be for a duration of two years from first study treatment. At the completion of two years of therapy, those subjects who are benefiting and still meet study criteria may continue after discussion and agreement between the Investigator and Medical Monitor (See Section 4.3.7).

Study Phase: Exploratory

Research Hypothesis: It is hypothesized that nivolumab (an anti-Programmed Cell Death-1 (PD-1) monoclonal antibody), and nivolumab in combination with ipilimumab will produce pharmacodynamic changes in the peripheral blood and tumor tissue of subjects with advanced melanoma (unresectable or metastatic).

Primary Objective:

To investigate the pharmacodynamic activity of nivolumab, and nivolumab in combination with ipilimumab in the tumor environment and the periphery on biomarker measures such as circulating T cell subsets (activated and memory T cell populations by flow cytometry), interferon, interferon inducible factors and T cell (CD4 and CD8) infiltration in tumor biopsy sections from subjects with advanced melanoma.

Secondary Objectives:

- To further describe the safety and tolerability of nivolumab and nivolumab in combination with ipilimumab in subjects with advanced melanoma
- To further describe the preliminary anti-tumor activity of nivolumab and nivolumab in combination with ipilimumab in subjects with advanced melanoma
- To further investigate the immunogenicity of nivolumab and ipilimumab
- To assess the potential association between PD-L1 expression (by IHC) and clinical efficacy measures

[redacted]

Study Design: This is an exploratory, open-label, multicenter study of nivolumab (which is a fully human monoclonal IgG4κ antibody targeting PD-1 (CD279)), and nivolumab in combination with ipilimumab.

Approximately 150 subjects with advanced melanoma (unresectable or metastatic) will be treated in this study in four (4) parts. Part 1 of this study will have two (2) cohorts consisting of approximately 40 patients each: cohort 1 will consist of anti-CTLA4 therapy-naive patients and cohort 2 will consist of patients who have progressed on an anti-CTLA-4 regimen. Cohorts 1 and 2 will be administered nivolumab at the 3mg/kg dose level every 2 weeks. In this part of the study, patients will go through a screening period of no longer than 28 days and eligible patients will start the treatment period for a duration of 2 years depending on their response. Nivolumab will be administered by IV infusion every 14 days in 56 day cycles (on days 1, 15, 29 and 43 of each cycle). Response assessments will be performed on days 49-56. The response assessment must be completed before the first dose in the next cycle.
In the second part of this study, approximately 20 anti-CTLA4 therapy-naive patients with matched pre- and on-treatment tumor biopsies will be administered nivolumab at 1 mg/kg and ipilimumab at 3 mg/kg every 3 weeks for 4 doses followed by nivolumab 3 mg/kg alone every 2 weeks (Arm A). This part of the study is aimed at defining the optimal window for on-treatment biopsy with concurrent nivolumab and ipilimumab therapy. Two (2) groups of approximately 10 patients each will be enrolled sequentially with the first group assigned to an on-treatment biopsy between Days 8 and 15 (weeks 2 and 3) after the start of therapy and the second group assigned to an on-treatment biopsy between Days 22 and 29 (subsequent to the second dose of therapy between weeks 4 and 5) after the start of therapy. Optimal biopsy timing will be defined as the biopsy window with the greatest pharmacodynamic increase in intratumoral activated T cells compared to the pre-treatment biopsy. The defined optimal on-treatment biopsy window will be used in the third part of this study.

In the third part of this study, approximately 30 anti-CTLA4 therapy-naive patients will be randomized 2:1 and treated with one of the following:

- Arm A: nivolumab 1 mg/kg IV combined with ipilimumab 3 mg/kg IV Q3W for 4 doses then nivolumab 3 mg/kg IV Q2W
- Arm B: nivolumab 3 mg/kg IV Q2W

In the fourth part of this study, approximately 20 anti-CTLA4 therapy-naive patients with brain metastases will be randomized 1:1 and treated with one of the following:

- Arm D: nivolumab 1 mg/kg IV combined with ipilimumab 3 mg/kg IV Q3W for 4 doses then nivolumab 3 mg/kg IV Q2W
- Arm E: nivolumab 3 mg/kg IV Q2W

In Parts 2, 3 and 4 of this study, patients will also go through a screening period of no longer than 28 days. In Parts 2 and 3, pre-treatment samples will be centrally assessed for tumor content and subjects who have samples with insufficient tumor content (≤ 100 tumor cells in a 4 micron tissue section) will require re-biopsy or will not be treated. In Part 4, tumor biopsy collection is optional, but strongly encouraged, if clinically safe. Eligible subjects will then start the treatment period for a duration of two years of therapy. Subjects randomized to Arm C in Part 3 of this study prior to the closure of this Arm have the option to receive nivolumab monotherapy upon consultation with the medical monitor. Response assessments will be performed approximately every 8 weeks (may differ by several weeks depending on treatment arm). The response assessment must be completed before the first dose in the next treatment visit.

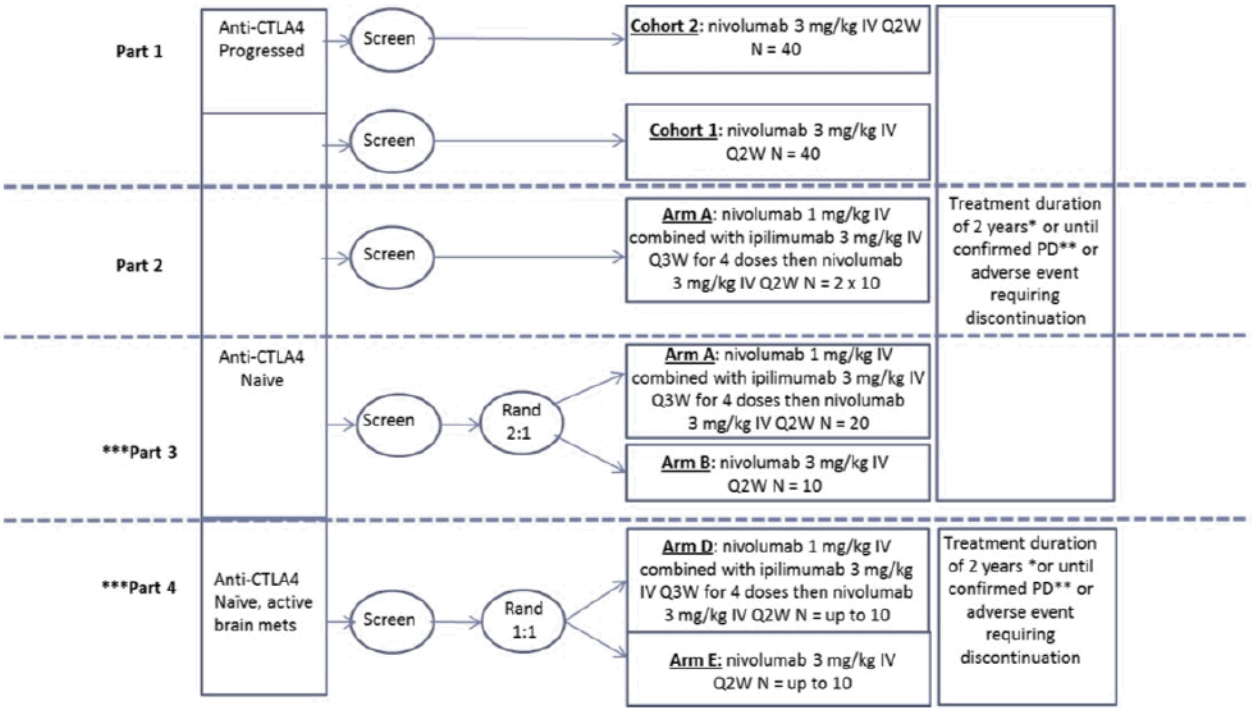
A study schema is presented below in Figure 1.

At the completion of 2 years of therapy, those subjects who are benefiting and still meet study criteria may continue after discussion and agreement between the investigator and Medical Monitor and will enter the Extension Period (See Section 4.3.7).

Subsequent to a duration of 2 years of active treatment or following the last dose of treatment in the Extension Period, each patient will continue follow-up consisting of office visits, lab work and tumor assessments for a maximum period of up to 100 days; follow-up office visits 1 and 2 (40-60 days and 101-120 days after the stop of study therapy). Completion of subsequent follow-up office visits will depend on the status of the subject at the end of the treatment period.

All patients who have not completed 2 years of treatment will be followed for overall survival assessment by telephone contact every 3 months from the last follow-up office visit for the remainder of time left to complete 2 years from the first dose of treatment. Patients that enter the Extension Period will be followed for overall survival assessments up to a maximum of 100 days after the last treatment dose.

Figure 1: Study Schema



* At the completion of two years of therapy, those subjects who are benefiting and meet criteria may continue after discussion and agreement between the Investigator and Medical Monitor and will enter the Extension Period (See Section 4.3.7).

**Subjects may be treated beyond PD, refer to Section 4.3.8

***In Parts 3 and 4, infusion times for nivolumab and ipilimumab will be as follows:

- nivolumab (3 mg/kg) monotherapy will be infused over 30 minutes
- for the combination, nivolumab (1 mg/kg) will be infused over 30 minutes and after a 30-minute break, ipilimumab (3 mg/kg) will be infused over 30 minutes, then nivolumab (3 mg/kg) will be infused over 30 minutes

Duration of Study: The study is expected to accrue over a period of approximately 2 years.

– maximum 28 days of screening

- At the completion of 2 years of therapy, those subjects who are benefiting and still meet study criteria may continue after discussion and agreement between the investigator and Medical Monitor and will enter the Extension Period (See Section 4.3.7).
- approximately 3 months follow-up office visits (including tumor assessments)
- 2 year overall survival assessment (by telephone contact) from first therapy dose for time remaining from the last follow up office visit or for those patients that enter the Extension Period, overall survival assessments will be continued for 100 days following the last treatment dose.

Number of Subjects: approximately 150 subjects will be treated

Estimated Enrollment: approximately 200 subjects will be screened (25% screen fail rate)

Study Population: The study population will include men and women age 16 or older with a histological diagnosis of advanced melanoma (unresectable or metastatic). All subjects must have measurable disease. Subjects must also have accessible tumor that can be biopsied at acceptable clinical risk (as judged by the investigator, with the exception of subjects with brain metastases enrolled in Arms D and E) and must consent to pre-treatment and on-treatment tumor biopsies. Tumor biopsy sites must be distinct from evaluable lesions and not have been irradiated prior to entry. Cohort 1 and Arms A, B, D and E will consist of subjects who are anti-CTLA-4 therapy naive and cohort 2 will consist of subjects who have progressed on anti-CTLA-4 therapy.

Women of childbearing potential must not be nursing or pregnant and must be using an acceptable method of contraception for at least 4 weeks before dosing. All women must have a negative pregnancy test within 24 hours prior to dosing with study medication.

Study Assessments:

Safety Outcome Measures: Safety assessments will be based on the medical review of adverse event reports, results of vital sign measurements, Eastern Cooperative Oncology Group (ECOG) performance status, physical examinations, clinical laboratory results, ECGs, and imaging tests.

The incidence of observed adverse events will be categorized using the most current version of MedDRA and reviewed for potential significance and clinical importance. Adverse events will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0

Efficacy Measures: Disease evaluation with computed tomography (CT) and/or magnetic resonance imaging (MRI), as appropriate, will be performed at baseline, and then approximately every 8 weeks until disease progression or treatment discontinuation (whichever happens later). Tumor response will be determined for all subjects as defined by RECIST 1.1. At the sponsor's discretion, scans and measurements may be reviewed by independent radiologists using RECIST 1.1 criteria at a later date or any time during the study. In the absence of clinical deterioration, any initial assessment of progressive disease (PD) will be confirmed by a repeat evaluation at the next tumor assessment time point, but no sooner than 4 weeks later.

Pharmacokinetic (PK) Measures: Serum concentrations of nivolumab and ipilimumab will be assessed at on-treatment and follow-up office visits as specified in Tables 5.5.A, 5.5C, 5.5D, and 5.5E. PK parameters for nivolumab and ipilimumab will be derived from serum concentration versus time data.

[redacted]

Statistical Considerations:

Sample size:

The primary objective of this study is to assess the pharmacodynamic activity of immunomodulatory biomarkers following treatment with nivolumab and nivolumab in combination with ipilimumab. It is of interest to ensure precision of the estimate of the ratio of on-treatment biomarker assessments to baseline levels in part 1 cohort 1 and 2. Assuming that a biomarker is measured as a continuous variable, 40 subjects per cohort will provide the following confidence that the estimate of the ratio of on-treatment to baseline values will be within 20% of the true value:

Table 1:	**Probability that estimated ratio of on-treatment to baseline value is within 20% of true value**						
Intra-subject Standard deviation (log-scale)	0.20	0.30	0.40	0.50	0.60	0.70	0.80
Probability	100%	100%	97%	93%	86%	80%	74%

For example, for a biomarker with an intra-subject standard deviation of 0.5, if the true ratio of post-baseline to baseline geometric means is 1.2 (increase from baseline is 20%), there is 93% probability that the estimated ratio would be within 0.96 and 1.44 (or a percent change between -4% and 44%). If the true increase from baseline is 60%, for a biomarker with the same variability, then there is 93% probability that the estimated percent change would be between 28% and 92%.

More specifically, preliminary data analysis of activated and memory CD4 and CD8 T cells in CA209-003 project an intra-subject standard deviation on the log scale between 0.5 and 0.6. Assuming this variability estimate is applicable to this study, there is 86%-93% probability that the geometric mean ratio of on-treatment to baseline T cell subset levels will be within 20% of their true value.

It is of interest to ensure precision of the estimate of the proportion of subjects with increased activated T cells on-treatment (at optimal window for biopsy) in part 2 and 3 Arms A and B. With a total of 30 subjects (from part 2 and part 3) treated in Arm A (with biopsy collected at optimal on-treatment window), the maximum width of the exact 2-sided 95% confidence interval (CI) is 37% when the proportion of subjects with increased activated T cells is expected to be in the 20% to 60% range. The 95% exact CIs are presented in Table 2.

Table 2:	**95% Exact CI for Proportion of Subjects with Increased Activated T Cell On-treatment**				
Proportion	20%	30%	40%	50%	60%
95% Exact CI	(7.7%, 38.6%)	(14.7%, 49.4%)	(22.7%, 59.4%)	(31.3%, 68.7%)	(40.6%, 77.3%)

With a total of 10 subjects treated in Arm B (with biopsy collected at optimal on-treatment window), the maximum width of the exact 2-sided 95% confidence interval (CI) is 59% when the proportion of subjects with increased activated T cells is expected to be in the 20% to 30% range. The 95% exact CIs are presented in Table 3.

Table 3:	**95% Exact CI for Proportion of Subjects with Increase Activated T Cell on-Treatment**	
Proportion	20%	30%
95% Exact CI	(2.5%, 55.6%)	(6.7%, 65.3%)

For example, if the observed proportion of subjects with increased activated T cells is 20% (data from CA184-004 indicate that ~25% of metastatic melanoma patients have an increase in intratumoral, activated T cells with ipilimumab alone), there is 95% probability that the exact CI (2.5, 55.6%) will cover the true proportion.

Approximately 10 subjects will be treated in Arm D and 10 subjects in Arm E to provide additional information regarding pharmacodynamic activity of immunomodulatory biomarkers following treatment with nivolumab and nivolumab in combination with ipilimumab. Administration of nivolumab and nivolumab in combination with ipilimumab to 10 subjects per arm provides 90% probability of observing at least one occurrence of any adverse event (or one response) that would occur with a 21% incidence in the population from which the sample is drawn.

Endpoints:

Safety: The incidence rate of adverse events, serious adverse events, deaths, hematologic laboratory abnormalities, serum chemistry laboratory abnormalities, and changes in blood pressure and heart rate measurements.

Efficacy: Best overall response (BOR), Objective response rate (ORR), duration of response and progression free survival rate (PFSR) at 24 weeks.

[redacted]

Analyses:

Safety: All recorded adverse events will be listed and tabulated by system organ class, preferred term, and cohort/arm and coded according to the most current version of MedDRA. The incidence of adverse events will be reviewed for potential significance and clinical importance. Vital signs and clinical laboratory test results will be listed and summarized by cohort/arm. Any significant physical examination findings and results of clinical laboratory tests will be listed. The incidence of infusion reactions will be reviewed to assess the safety and tolerability of reduced infusion times for nivolumab and nivolumab in combination with ipilimumab.

ECG readings will be evaluated by the investigator and abnormalities, if present, will be listed.

Efficacy: All available tumor measurement data will be listed. Individual best overall response (BOR) will be listed and tabulated by cohort/arm. The objective response rate (ORR), and corresponding 90% confidence intervals will be reported by cohort/arm.

Medians and corresponding two-sided 95% confidence intervals will be reported for duration of response, PFS, and OS by cohort and analyzed using Kaplan-Meier methods. Estimated PFS rate at 24 weeks (by Kaplan-Meier method) and 90% confidence intervals (based on Greenwood's formula) will be reported.

Efficacy analyses will be performed separately for the populations of all treated subjects and response-evaluable subjects.

Pharmacokinetic Analyses: Summary statistics for serum nivolumab and ipilimumab concentrations (including Cmin and Ceoinf) will be tabulated by cohort/arm, study day, and time. Summary statistics will be provided for pharmacokinetic parameters for nivolumab and ipilimumab (Cmax, AUC(0-T) and Tmax) by cohort/arm. In addition, pharmacokinetic data from this study may be combined with data from other studies for a population PK model which may be presented in a separate report.

[redacted]

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1.2 Research Hypothesis

It is hypothesized that nivolumab (an anti-Programmed Cell Death-1 (PD-1) monoclonal antibody) and nivolumab in combination with ipilimumab will produce pharmacodynamic changes in the peripheral blood and tumor tissue of subjects with advanced melanoma (unresectable or metastatic).

1.3 Objectives

1.3.1 Primary Objective

- To investigate the pharmacodynamic activity of nivolumab, and nivolumab in combination with ipilimumab in the tumor environment and the periphery on biomarker measures such as circulating T cell subsets (activated and memory T cell populations by flow cytometry), interferon, interferon inducible factors and T cell (CD4 and CD8) infiltration in tumor biopsy sections from subjects with advanced melanoma

1.3.2 Secondary Objectives:

- To further describe the safety and tolerability of nivolumab and nivolumab in combination with ipilimumab in subjects with advanced melanoma
- To further describe the preliminary anti-tumor activity of nivolumab and nivolumab in combination with ipilimumab in subjects with advanced melanoma
- To further investigate the immunogenicity of nivolumab and ipilimumab
- To assess the potential association between PD-L1 expression (by IHC) and clinical efficacy measures

- [redacted]

1.4 Product Development Background

The following sections provide a brief background on nivolumab and ipilimumab. Complete information on the pre-clinical pharmacology, toxicology, pharmacokinetics, and clinical safety and efficacy for these agents can be found in the respective Investigator Brochures (IB).[72, 37]

[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).

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

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

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s).

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

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have a written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects. The investigator or Sponsor should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling, information to be provided to subjects and any updates.

The investigator or Sponsor should provide the IRB/IEC with reports, updates and other information (e.g., 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 are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

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

Investigators must:

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

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

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

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. The explicit wish of a minor, who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

Minors who are judged to be of an age of reason must also give their written assent.

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

Study Design: This is an exploratory, open-label, multicenter study of nivolumab and nivolumab in combination with ipilimumab.

Approximately 150 subjects with advanced melanoma (unresectable or metastatic) will be treated in this study in four (4) parts. Part 1 of this study will have two (2) cohorts consisting of approximately 40 patients each: cohort 1 will consist of anti-CTLA4 therapy-naive patients and cohort 2 will consist of patients who have progressed on an anti-CTLA-4 regimen. Cohorts 1 and 2 will be administered nivolumab at 3 mg/kg dose level every 2 weeks. Subjects will go through a **screening period** of no longer than 28 days and eligible subjects will start the **treatment period** for a duration of 2 years depending on their response. Nivolumab will be administered by IV infusion every 14 days in 56 day cycles (on days 1, 15, 29 and 43 of each cycle)**.** Response assessments will be performed on days 49-56. The response assessment must be completed before the first dose in the next cycle.

In Part 2, approximately 20 anti-CTLA4 therapy-naive patients will be administered nivolumab at 1 mg/kg and ipilimumab at 3 mg/kg every 3 weeks for 4 doses, followed by nivolumab 3 mg/kg alone every 2 weeks (Arm A). This part of the study is aimed at defining the optimal window for on-treatment biopsy with concurrent nivolumab and ipilimumab therapy. All subjects will be required to undergo a pre-treatment biopsy and consent to on-treatment biopsy. Two (2) groups of approximately 10 patients each will be enrolled sequentially with the first group assigned to an on-treatment biopsy between Days 8 and 15 (weeks 2 and 3) after the start of therapy and the second group assigned to an on-treatment biopsy between Days 22 and 29 (subsequent to the second dose of therapy between weeks 4 and 5) after the start of therapy. Optimal biopsy timing will be defined as the biopsy window with the greatest pharmacodynamic

increase in intratumoral activated T cells compared to the pre-treatment biopsy. The defined optimal on-treatment biopsy window will be used in the third part of this study.

In Part 3, approximately 30 anti-CTLA4 therapy-naive patients will be randomized 2:1 and treated with one of the following:

- Arm A: nivolumab 1 mg/kg IV combined with ipilimumab 3 mg/kg IV Q3W for 4 doses then nivolumab 3 mg/kg IV Q2W
- Arm B: nivolumab 3 mg/kg IV Q2W

In Part 4, approximately 20 anti-CTLA4 therapy-naive patients with brain metastases will be randomized 1:1 and treated with one of the following:

- Arm D: nivolumab 1 mg/kg IV combined with ipilimumab 3 mg/kg IV Q3W for 4 doses then nivolumab 3 mg/kg IV Q2W
- Arm E: nivolumab 3 mg/kg IV Q2W

In Parts 2, 3 and 4 of this study, patients will also go through a screening period of no longer than 28 days. In Parts 2 and 3, pre-treatment samples will be centrally assessed for tumor content and subjects who have samples with insufficient tumor content ($\leq$ 100 tumor cells in a 4 micron tissue section) will require re-biopsy or will not be treated. In Part 4, tumor biopsy collection is optional, but strongly encouraged if clinically safe. Eligible subjects will then start the treatment period for a maximum of two years of therapy. Subjects randomized to Arm C in Part 3 of this study prior to the closure of this Arm have the option to receive nivolumab monotherapy upon consultation with the medical monitor.

Response assessments will be performed approximately every 8 weeks (may differ by several weeks depending on treatment arm). The response assessment must be completed before the first dose in the next treatment visit.

A study schema is presented below in Figure 3.1.

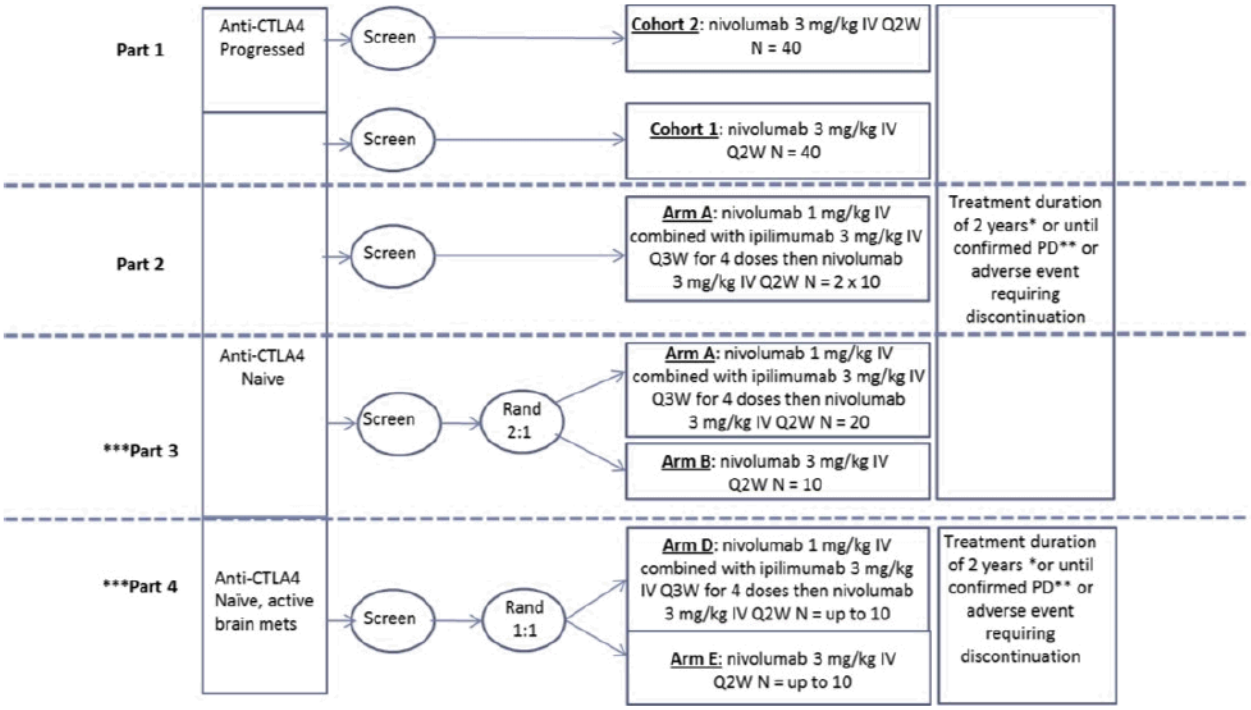
At the completion of 2 years of therapy, those subjects who are benefiting and still meet study criteria may continue after discussion and agreement between the investigator and Medical Monitor and will enter the Extension Period (See Section 4.3.7). Treatment in the Extension Period will continue until progression of disease or unacceptable toxicity.

Subsequent to a duration of 2 years of active treatment or following the last dose of treatment in the Extension Period, each patient will continue **follow-up** consisting of office visits, lab work and tumor assessments for a maximum period of up to 100 days; follow-up office visits 1 and 2 (40-60 days and 101-120 days after the stop of study therapy). Completion of subsequent follow-up office visits will depend on the status of the subject at the end of the treatment period.

Patients with confirmed disease progression as described in Sections 1.1.9 and 4.3.8 will complete follow-up office visits 1 and 2 and will then continue follow-up by **telephone assessment** every 3 months for the remainder of time left to complete 2 years from the first dose of treatment.

All patients will be followed for overall survival assessment by telephone contact every 3 months from the last follow-up office visit for the remainder of time left to complete 2 years from the first dose of therapy. Patients that enter the Extension Period will be followed for overall survival assessments up to a maximum of 100 days after the last treatment dose.

Figure 3.1: Study schema



* At the completion of two years of therapy, those subjects who are benefiting and meet criteria may continue after discussion and agreement between the Investigator and Medical Monitor and will enter the Extension Period (See Section 4.3.7).

Subjects may be treated beyond PD, refer to Section 4.3.8*In Parts 3 and 4:

- nivolumab (3 mg/kg) as monotherapy will be infused over 30 minutes
- for the combination, nivolumab (1 mg/kg) will be infused over 30 minutes and after a 30-minute break, ipilimumab (3 mg/kg) will be infused over 30 minutes, then nivolumab (3mg/kg) will be infused over 30 minutes

Number of Subjects: approximately 150 subjects treated

Duration of Study: The study is expected to accrue over a period of approximately 2 years.

- maximum 28 days of screening
- At the completion of 2 years of therapy, those subjects who are benefiting and still meet study criteria may continue after discussion and agreement between the investigator and Medical Monitor and will enter the Extension Period (See Section 4.3.7)
- approximately 3 months follow-up office visits (including tumor assessments)

– 2 year overall survival assessment (by telephone contact) from first therapy dose for time remaining from last follow up office visit or for those patients that enter the Extension Period, overall survival assessments will be continued for 100 days following the last treatment dose.

3.2 Post Study Access to Therapy

Not applicable for this study

3.3 Study Population

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to ensure that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria. No exceptions will be granted.

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

3.3.1 Inclusion Criteria

1) Informed Consent:

a) Signed, written Informed Consent must be obtained prior to the performance of any study related procedures that are not considered part of standard of care

2) Target Population:

a) Subjects with advanced melanoma (unresectable or metastatic) who have received and either progressed or discontinued on no more than 3 prior treatment regimens or have refused standard therapy for treatment of metastatic melanoma.

i. Subjects may have been treated or offered treatments for melanoma (e.g., chemotherapy, biological therapy, targeted therapy, vaccine therapy or cytokine therapy).

ii. Subjects who have never received any treatment for metastatic disease, ie. newly diagnosed subjects, may be allowed on study if they have been offered and have refused standard therapy or are deemed to be inappropriate candidates for standard therapy by the investigator.

iii. Subjects enrolled to Cohort 1 and Arms A, B, D and E (see Figure 3.1) must never have received anti-CTLA4 therapy (anti-CTLA4 naive).

iv. Subjects enrolled to cohort 2 (see Figure 3.1) must have had anti-CTLA4 monoclonal antibody (mAb) based therapy as 1 of the prior regimens (anti-CTLA4 progressors). If anti-CTLA4 mAb therapy was the last treatment regimen prior to study entry, the last dose of anti-CLTA4 mAb must have been administered at least 6 weeks prior to initiation of study therapy. Relapse during or within 6 month of last dose of anti-CTLA4 mAb adjuvant treatment for completely resected melanoma alone will also fulfill this criterion.

v. Subjects enrolled to Arms D and E

(1) Must have at least one measurable index brain metastases > 0.5 cm and not larger than 3 cm that has not been previously irradiated

(2) Index brain lesions must not have sequela of prior therapy that would confound attribution of tumor response including edema or hemorrhage
(3) Must not have neurologic symptoms secondary to metastatic lesions
(4) Must not have received systemic corticosteroids within 14 days prior to initiation of study therapy.

b) Subjects must have histologic confirmation of advanced melanoma. Confirmation of diagnosis must be obtained from the pre-treatment biopsy if it is not available from a prior diagnostic procedure.
c) Subjects must consent to allow the acquisition of existing (archival) formalin-fixed paraffin-embedded (FFPE) material (block or a minimum of 10 unstained slides) for performance of correlative studies.
d) Subjects must have at least one measurable lesion at baseline by CT or MRI as per RECIST 1.1criteria (see Appendix 2).
    i. Tumor sites used to satisfy this criterion must not have received any prior radiation therapy.
    ii. Sites for biopsy must be distinct from target lesions used for efficacy assessment.
e) Subjects must have at least 1 tumor site that can be biopsied at acceptable clinical risk, as judged by the Investigator, and must consent to pre-treatment and on-treatment tumor biopsies. For Part 4, pre-treatment and on-treatment biopsies are optional, but strongly encouraged.
    i. Lesions should not have received prior radiation therapy
    ii. These sites must be designated for biopsy prior to the first treatment, to avoid selection bias that may affect study endpoints.
    iii. In Part 1, pathologic confirmation of viable tumor cells (touch imprint cytopathology) from collected tissue samples is strongly recommended to permit consideration of repeat biopsy if deemed of acceptable clinical risk. Subjects for whom pre-treatment adequate tissue biopsy (demonstration of tumor cells on touch prep) cannot be achieved may still remain on study and continue to receive study therapy and undergo other sample collections. However, that subject will then be replaced.
    iv. In Parts 2 and 3, pre-treatment tumor samples must contain sufficient tumor content (≤100 tumor cells/4-micron tissue section) upon central assessment. If sample contains insufficient tumor content, a re-biopsy will be required to obtain a sample with sufficient tumor content prior to treatment.
    v. The site of biopsy should not include lymph nodes in Parts 2, 3 and 4.
f) Subjects must have ECOG performance status ≤1 (See Appendix 1).
g) Subjects must have the ability to comply with treatment, PK, biomarker sample collection, and required study follow-up.
h) Organ and marrow function as follows (blood product transfusion is not permitted in the 4 weeks prior to achieve entry criteria):
    i. White blood cell count ≥ 2,000 cells/mm^3

ii. Neutrophils ≥ 1500/μL (stable, off any growth factor for at least 4 weeks prior to study drug administration)

iii. Platelet count ≥ 100,000/mm^3

iv. Hemoglobin ≥ 9.0 g/dL

v. Total bilirubin ≤ 1.5x the institutional upper limit of normal (IULN)

vi. Subjects with Gilbert's syndrome are eligible if their total bilirubin is less than 3.0 mg/dl

vii. ALT (alanine aminotransferase) and AST (aspartate aminotransferase) ≤ 3x IULN

viii. Estimated GFR (eGFR) calculated via MDRD or Cockcroft-Gault equations ≥ 40 mL/min

i) Known BRAF V600 mutation status (Parts 2, 3 and 4). Subjects with either V600 wild-type or V600 mutation-positive status, are eligible.

3) Age and Reproductive Status:

a) Males and females ≥ 16 years of age.

b) Women of childbearing potential:

i. Women of childbearing potential (WOCBP) must use method(s) of contraception based on the tables in Appendix 3. A highly effective method(s) of contraception (failure rate of less than 1% per year) is required. The individual methods of contraception should be determined in consultation with the investigator. WOCBP must follow instructions for birth control when the half life of the investigational drug is greater than 24 hours, contraception should be continued for a period of 30 days plus the time required for the investigational drug to undergo five half lives (total of 23 weeks after the last dose of investigational product).

ii. Women 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 investigational product.

iii. Women must not be breastfeeding.

c) Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. Men that are sexually active with WOCBP must follow instructions for birth control when the half life of the investigational drug is greater than 24 hours, contraception should be continued for a period of 90 days plus the time required for the investigational drug to undergo five half lives (total of 31 weeks after the last dose of investigational product).

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

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Cohort 1 and 2, Arms A and B: Active CNS metastases (including evidence of cerebral edema by CT scan or MRI, progression from prior imaging study, any requirement for steroids or clinical symptoms of/from CNS metastases) within 28 days of study enrollment.

b) Cohort 1 and 2, Arms A and B: Subjects with known metastases must have a repeat imaging brain scan within 28 days of randomization/registration. If progression in prior lesion(s) or new lesion(s) is/are detected on repeat brain scan, patients are excluded from study.

c) Arms D and E: History of carcinomatous meningitis (lumbar puncture is not required).

d) Arms D and E: Radiation within 14 days prior to initiation of study therapy, and the radiation field cannot have included the index brain lesion.

2) Medical History and Concurrent Diseases

a) Participation in a blinded trial or study which has not yet completed final database lock and has not been unblinded for primary endpoint analysis

b) Subjects with other concomitant malignancies, except basal cell or squamous cell skin cancers, superficial bladder cancer, or carcinoma in situ of the cervix or breast, are excluded unless a complete remission was achieved at least 2 years prior to study entry and no additional therapy is required or anticipated to be required during the study period

c) Subjects with active autoimmune disease, a history of known or suspected autoimmune disease or a history of a syndrome requiring systemic corticosteroids (> 10 mg daily prednisone equivalent), cytotoxic therapy or immunosuppressive medications with the exception of:

i. Isolated vitiligo

ii. Resolved childhood atopy

iii. The history of positive ANA titer without associated symptoms or history of symptoms of an autoimmune disorder

iv. Controlled thyroid disorders

d) Positive tests for human immunodeficiency virus (HIV 1/2) antibody (may obtain additional testing or substitute testing per institutional guidelines to rule out infection), or known acquired immunodeficiency syndrome (AIDS)

e) History of any chronic hepatitis including alcoholic, non-alcoholic steatohepatitis (NASH), drug related, autoimmune, chronic viral

i. Positive tests for hepatitis B virus surface antigen (HBsAg) or

ii. hepatitis C antibody (may obtain additional testing or substitute testing per institutional guidelines to rule out infections)

f) Evidence of active infection ≤ 7 days prior to initiation of study drug therapy.

g) Prior organ allograft or allogenic bone marrow transplantation.

h) Uncontrolled or significant cardiovascular disease including, but not limited to, any of the following:
   i. Myocardial infarction within the past 6 months
   ii. Uncontrolled angina within the past 3 months
   iii. History (family or personal) of congenital long QT syndrome
   iv. Any history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation or Torsades de pointes)
   v. Controlled atrial fibrillation by itself is not an exclusion criterion
   vi. History of other clinically significant heart disease (i.e. cardiomyopathy, NYHA functional classification III-IV)
   vii. Requirement for daily supplemental oxygen therapy

i) Known or underlying medical condition (e.g., a condition associated with diarrhea, diverticulitis, neuropathy or atopy) that, in the Investigator's opinion, would make the administration of study drug hazardous to the subjects or obscure the interpretation of toxicity determination or adverse events

j) Subjects with evidence of bleeding disorder deemed unsafe by the Investigator to undergo biopsies

k) Subjects who are unable to undergo venipuncture and/or to tolerate venous access.

l) Subjects who have undergone any major surgery within 4 weeks of study drug administration

m) Subjects with psychiatric illness or social situations that would preclude study compliance or the ability to tolerate study procedures and or study therapy.

n) Subjects with the presence of underlying medical condition that in the opinion of the Investigator or Sponsor could adversely affect the ability of the subject to comply with or tolerate study procedures and/or study therapy

3) Allergies and Adverse Drug Reaction

a) History of allergy to components of the study drug or known allergy to antibody therapies

b) Subjects with a known history of the following anti-CTLA4 therapy related adverse reactions based on the CTCAE v4.0 criteria:
   i. Any ≥ grade 3 anti-CTLA4 mAb related dose-limiting adverse reaction
   ii. Any anti-CTLA4 mAb related event requiring permanent discontinuation of therapy regardless of grade
   iii. Any adverse reaction that did not resolve with steroids alone (i.e. required infliximab, mycophenolate or cyclophosphamide)
   iv. Any Grade ≥ 3 non-laboratory anti-CTLA4 therapy related adverse reaction except for:
      (a) Endocrinopathies where clinical symptoms were controlled with appropriate hormone replacement therapy
      (b) Nausea
      (c) Fatigue

v. Any Grade ≥3 laboratory abnormalities except for:

(a) Any Grade ≥3 lymphopenia

(b) Any transient Grade ≥3 electrolyte abnormalities that occurred while on anti-CTLA4 therapy that were not associated with clinical symptoms and responded with 72 hours

(c) Any AST, ALT or T. bilirubin such that:

(i) AST or ALT > 10 x ULN

(ii) Total bilirubin > 5 x ULN

vi. Any ≥ Grade 2 eye pain or reduction of visual acuity that did not respond to topical therapy and did not improve to ≤ Grade 1 severity within 2 weeks of starting topical therapy or required systemic treatment.

vii. History of Grade ≥ 3 neurologic toxicity

4) Sex and Reproductive Status

a) WOCBP who are **unwilling or unable** to use an acceptable method to minimize the risk of pregnancy for the entire study period and for at least 23 weeks after the last dose of investigational product.

b) Women who are pregnant or breastfeeding.

c) Women with a positive pregnancy test on enrollment or prior to investigational product administration.

d) Sexually active fertile men not using effective birth control when their partners are WOCBP for at least 31 weeks after the last dose of investigational product.

5) Prohibited Prior Treatments and/or Therapies

a) Subjects who have received prior treatment with T cell coregulatory protein targeted therapies including but not limited to, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-OX-40, anti-CD40 in the adjuvant or metastatic setting are ineligible to participate in the study. Prior anti-CTLA4 monoclonal antibody therapy is permitted for cohort 2.

i. Prior cytokine therapy **is** allowed (e.g. interferon or interleukin-2).

b) Exposure to any other investigational drug within 4 weeks of study drug administration

c) Any anti-cancer therapy (e.g., chemotherapy, biologics, vaccines, radiotherapy, or hormonal treatment) within 5 half lives or within a maximum of 4 weeks of study drug administration (if 5 half-lives is longer than 4 weeks)

d) Use of non-oncology vaccines (live, attenuated, or inactivated) against infectious diseases (for example, MMR, polio, Pneumovax®, Zostavax®. Flumist®) within 4 weeks (28 days) of initiation of study therapy

i. Use of the seasonal killed influenza vaccine is allowed without restriction.

e) Use of growth factors, including, but not limited to, granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF) or erythropoietin within 4 weeks of study drug therapy

f) Use of pRBC or platelet transfusion 4 weeks prior to study drug therapy

g) Systemic corticosteroids must be ≤ 10 mg daily prednisone equivalents 4 weeks before the first dose of study therapy. Subjects requiring long term immunosuppression are not eligible.

h) Use of anti-RANKL therapy (i.e. denosumab as Xgeva® or Prolia®) within 140 days (5 half-lives) prior to study drug administration

i) Use of oral or intravenous bisphosphonate therapy (e.g. zolendronic acid, alendronate or risedronate) less than 5 half-lives prior to study drug administration

j) Use of herbal over-the-counter (OTC) supplements is not permitted. Concerns regarding specific OTC therapies may be discussed with the medical monitor.

6) Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated

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

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

No exceptions to these criteria will be granted by the Sponsor.

3.3.3 Women of Childbearing Potential

A Woman 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 must have a serum follicle stimulating hormone, (FSH) level > 40mIU/mL to confirm menopause.

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

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

Other parenteral products may require as long as 6 months.

3.4 Concomitant Treatments

All medications taken within 28 days before the administration of study drug and all concomitant therapy administered during the study will be recorded on the relevant CRF, along with the reasons for and details of therapy use.

3.4.1 Prohibited and/or Restricted Treatments

1) Concurrent chemotherapy, hormonal therapy, immunotherapy regimens, or radiation therapy, standard or investigational. Exceptions include:
   a) Palliative or supportive care may be offered to all subjects.
   b) Palliative/therapeutic therapies (e.g., focal radiotherapy for pain or bone metastases, thoracocentesis or paracentesis for comfort) may be administered after consultation with the Medical Monitor.
   c) Palliative radiation therapy for bone metastases is permitted, but subjects should not receive study treatment during radiation and must meet re-treatment criteria prior to resuming treatment.
   d) Treatment of isolated symptomatic lesions by local surgery is permitted for palliative or potentially curative management at any time. All interventions should be discussed in advance with the BMS Medical Monitor. All tumor tissue that is not required for clinical pathology will be sent to BMS.
   e) A new biopsy will not be required for resuming re-treatment in the setting of interrupted active treatment for local palliative therapies, although it is encouraged, if considered safe by the investigator. All tumor tissue that is not required for clinical pathology will be sent to BMS.
2) Use of growth factors including, but not limited to, granulocyte colony stimulating factor (G-CSF), granulocyte macrophage colony stimulating factor (GM-CSF), or erythropoietin stimulating agents are not permitted, unless deemed necessary by investigator and discussed with medical monitor.
3) Use of systemic corticosteroids at > 10 mg daily prednisone equivalent, unless required for the treatment of infusion reactions, other adverse events, or for palliation as determined by the investigator.
4) Use of RANKL therapy unless required for management of osteolytic bone lesions, other adverse events or for palliation and after a discussion between the investigator and the medical monitor. Since RANKL therapy is a recognized immune modulator, **discussion must occur before starting any patient on RANKL therapy**.
5) Use of bisphosphate therapy, unless required for management of osteolytic bone lesions, adverse events or for palliation and after a discussion between the investigator and the medical monitor. Since bisphonates are recognized as immune modulators, **discussion must occur before starting any patient on bisphosphonate therapy**.
6) Steroids must not be given as prophylactic anti-emetic therapy.
7) Use of herbal remedies is not permitted

Use of prescription and over-the-counter medications (except medications from categories outlined above) is permitted at the discretion of the Investigator and must be recorded on CRF.

3.4.2 Other Restrictions and Precautions

None

3.4.3 Permitted Therapy

Subjects are permitted the use of topical, ocular, intranasal, intra-articular, and inhalational corticosteroids (with minimal systemic absorption). Immunosuppressive doses (e.g., prednisone > 10 mg/day or equivalent) and/or physiologic replacement doses of systemic corticosteroids (e.g., prednisone ≤ 10 mg/day) are permitted in the context of treating adverse events. A brief course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

Prophylactic anti-emetics, with the exception of steroids, may be administered at the discretion of the treating physician before any doses of study drug.

Use of the seasonal killed influenza vaccine during therapy is permitted without restriction. However, influenza vaccines containing live attenuated virus (Flumist ®) or other clinically indicated vaccinations for infectious diseases (killed or attenuated, e.g., Pneumovax ®, varicella, MMR, etc) may be permitted, but must be discussed with the Sponsor's Medical Monitor and may require a study drug washout period prior to and after administration of the vaccine.

3.5 Discontinuation of Subjects From Treatment

3.5.1 Permanent Discontinuation Criteria of Subjects from Treatment

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

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- 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 as per Section 4.3.5
- Pregnancy
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- Subjects should discontinue study therapy upon evidence of further disease progression, defined as an additional 10% or greater increase in tumor burden volume from the time of initial progression (including all target lesions and new measurable lesions), as per Section 4.3.8
- Clinical deterioration while receiving active study therapy.
- Inability to comply with the protocol

All subjects who discontinue should comply with protocol specified follow-up procedures as outlined in Section 3.1. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study treatment is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate case report form (CRF) page.

3.6 Post Treatment Study Follow-up

Subjects who discontinue study treatment may continue to be followed. Please refer to Section 3.1 and Tables in Section 5.1 for details.

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study treatment will remain in the study and must continue to be followed for 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**, whenever 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 BMS-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. 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 TREATMENTS

All protocol-specified investigational and non-investigational products are considered study drug.

4.1 Study Treatments

Treatment administration for nivolumab and ipilimumab (a ±2-day window will be allowed):

Table 4.1-1: Treatment Administration

Cohort/Arm	Dose	Infusion Time
1 and 2	3 mg/kg nivolumab every 2 weeks	60 minutes
A	1 mg/kg nivolumab + 3 mg/kg ipilimumab every 3 weeks x 4 doses and then 3 mg/kg nivolumab every 2 weeks	**Part 2**: nivolumab 60 minutes + 30 minutes break ipilimumab 90 minutes and then nivolumab 60 minutes
		Part 3: nivolumab 30 minutes + 30 minutes break ipilimumab 30 minutes and then nivolumab 30 minutes
B	3 mg/kg nivolumab every 2 weeks	30 minutes
D	1 mg/kg nivolumab + 3 mg/kg ipilimumab every 3 weeks x 4 doses and then 3 mg/kg nivolumab every 2 weeks	nivolumab 30 minutes + 30 minutes break ipilimumab 30 minutes and then nivolumab 30 minutes
E	3 mg/kg nivolumab every 2 weeks	30 minutes

Table 4.1-2: Product Description

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
BMS-936558-01 Solution for Injection	100 mg (10mg/mL)	10 mL/ open label	10 vials per box/ open labels	Colorless to pale yellow, clear to opalescent solution; may contain particles	Store Refrigerated, 2-8° C (36-46 F) Protect from light and freezing.
Ipilimumab Solution for Injection	200 mg (5 mg/mL)	40 mL per vial/Open-label	4 vials per carton/Open-label	Clear, colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect from light and freezing.

4.1.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined as follows:

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) in a way different from the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

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

In this protocol, the investigational products are: nivolumab and ipilimumab

The sites will be responsible to procure IV bags, diluents, and micron in-line filters (ie 0.2/ 0.22 micron; see current nivolumab and ipilimumab Investigator Brochure for required filter details)

4.1.2 Non-investigational Product

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

In this protocol, non-investigational product(s) are not applicable.

4.1.3 Handling and Dispensing

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

4.1.4 Nivolumab Vial Storage

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 the sponsor. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug. Contact the sponsor immediately. Nivolumab vials must be stored in the refrigerator at 2-8°C, protected from light and freezing. If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

After nivolumab has been prepared for administration, the total storage time (combination of refrigeration and room temperature exposure) is not to exceed 24 hours. For details on prepared drug storage and use time under room temperature/light and refrigeration, please refer to the

current nivolumab Investigator Brochure.[48] Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent.

4.1.5 Ipilimumab Vial Storage

For ipilimumab storage and administration instructions, please refer to the ipilimumab IB.

4.1.6 Study Drug Administration

Nivolumab is to be administered as an approximate 60 minute IV infusion in Parts 1 and 2, using a volumetric pump with a 0.2/0.22 micron in-line filter at the protocol-specified doses. It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline (per institutional standard of care). Details regarding the mixing and concentrations of the dose (preparation) and administration will be found in the current Investigator Brochure for nivolumab.[48]

Ipilimumab is to be administered as an approximate 90-minute IV infusion in Parts 1 and 2, using a volumetric pump with a 0.2 to 1.2 micron in-line filter at the protocol-specified dose. Care must be taken to assure sterility of the prepared solutions, since the drug product does not contain any antimicrobial preservatives or bacteriostatic agents. Please refer to the ipilimumab IB for further details regarding preparation/administration.

In Parts 3 and 4 of the study, the infusion times for nivolumab and ipilimumab will be shortened to 30 minutes each.

When both study drugs are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The 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 no sooner than 30 minutes after completion of the nivolumab infusion and after the post-nivolumab pharmacokinetic blood sample is drawn.

4.2 Method of Assigning Subject Identification

CA209038 is an open-label study. All enrolled subjects will be assigned a subject number, starting with 00001 and increasing sequentially with each additional enrolled subject. The subject number will be assigned by the Sponsor via IVRS once the subject signs the informed consent form. Each subject will then be identified by a distinct patient identification number (PID) which is comprised of the site number and the subject number. The Investigator or designee will register the subject following the enrollment procedures established by BMS. The following information is required for registration:

- Date of birth
- Gender
- Diagnosis
- Date of Informed Consent
- Planned date of 1st dose

Subjects will undergo screening evaluations to determine eligibility within 28 days prior to dosing. The investigative site will contact the Sponsor via IVRS for treatment assignment once a subject is determined to be eligible for enrollment. Enrolled subjects meeting all eligibility criteria will be assigned to Cohort 1 or 2 depending on prior anti-CTLA4 therapy status. After Amendment 04, enrolled subjects meeting all eligibility criteria will be assigned to Arm A for Part 2. After the optimal timing of the biopsy has been determined in Part 2 then, enrolled subjects meeting all eligibility criteria will be randomly assigned to Arms A or B in a 2:1 ratio in Part 3. In parallel, enrolled subjects meeting all eligibility criteria will be randomly assigned to Arms D or E in a 1:1 ratio in Part 4.

Subjects who do not have both pre-treatment and on-treatment biopsy will be replaced. Subjects in Arms D and E may undergo optional biopsies, especially if they have lesions in locations other than the brain. Subjects in Arms D and E will not be replaced. Replacement subjects will receive the same treatment but will be assigned a new subject number.

Specific instructions regarding enrollment and randomization will be provided to the investigational sites in their training materials.

4.3 Selection and Timing of Dose for Each Subject

As described in Section 4.2, subjects will be assigned to a cohort/arm in the order they enter the study. The subjects enrolled prior to Amendment 04 will be assigned a patient identification number (PID) by IVRS and placed into 1 of 2 dose cohorts based on whether they have had prior anti-CTLA4 treatment. Subjects enrolled after Amendment 04 will be assigned a patient identification number (PID) by IVRS and placed into Arms A, B, D or E.

4.3.1 Dose Modifications

There will be no actual dose adjustments allowed for nivolumab or ipilimumab except for weight changes (an increase or decrease of ≥ 10% in weight) at the beginning of each cycle.

4.3.2 Intrasubject Dose Escalation

No intrasubject dose escalation will be allowed

4.3.3 Dose Reductions

Nivolumab and ipilimumab dose reductions are not permitted in this study.

4.3.4 Dose Delay Criteria

Study drug administration should be interrupted and increased monitoring of subjects should ensue if any of the following drug related adverse event(s) occurs:

- Any persistent grade ≥2 non laboratory non-skin drug related adverse event except for fatigue and weakness
- Any grade ≥2 endocrine drug-related adverse event
- Any grade ≥ 3 skin drug related adverse event

- Any Grade ≥ 3 drug-related laboratory abnormality (except lymphopenia, asymptomatic lipase or amylase increases, or any electrolyte abnormality without any clinical sequelae that is either spontaneously reversible or resolves with clinical management to grade 2 or less within 72 hours)
- ALT or AST > 3X ULN (treatment may resume when the AE resolves to Grade 1)
- Patients with pre-existing neurologic or opthalmologic anti-CTLA4 related adverse event who develop clinical symptoms leading to a 1 grade drug related shift (i.e. grade 1 to grade 2)
- Any AE, laboratory abnormality or inter-current illness which, in the judgment of the investigator, warrants skipping the dose of study medication

If dose delay is necessary, both nivolumab and ipilimumab must be delayed until treatment can resume. If a delay prevents subsequent infusion of ipilimumab, the dose of ipilimumab should be replaced as soon as possible. At least 19 days must elapse between the replacement dose of ipilimumab and the administration of the next dose of the combination.

The occurrence of clinically meaningful drug related AEs requires early recognition and prompt intervention. Management algorithms are available for suspected pulmonary, gastrointestinal, hepatic, renal, endocrine, neurological and skin toxicities. The recommendation is to follow the nivolumab IB adverse event algorithm. The algorithms can also be found on Appendix 4.

4.3.5 Study Drug Discontinuation Criteria due to Adverse Event(s)

Study drug administration must be discontinued if at least one of the following drug related adverse event(s) occurs:

- Any ≥ Grade 2 eye pain or reduction of visual acuity that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks of starting therapy OR requires systemic treatment;
- Any ≥ Grade 3 non laboratory drug-related adverse event with the exception of fatigue, and endocrine drug related AEs which are stable with hormone replacement therapy
- Any ≥ Grade 3 bronchospasm, hypersensitivity reaction, or infusion reaction;
- Any patient that experiences any grade allergic/infusion reaction while receiving study drug at a slower infusion rate and/or with premedication due to a prior allergic/infusion reaction
- Any drug-related Grade 4 laboratory abnormalities, (except lymphopenia, asymptomatic lipase or amylase increases, or any electrolyte abnormality without any clinical sequelae that is either spontaneously reversible or resolves with clinical management to grade 2 or less within 72 hours)

- Hepatoxicity as evidenced by any of the following:
  - AST or ALT > 5 - 10x ULN for >2 weeks
  - AST or ALT > 10 ULN
  - Total bilirubin > 5 x ULN
  - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 ULN (potential Hy's Law case)
- Any adverse event, laboratory abnormality or intercurrent illness, which in the judgment of the Investigator, presents a substantial clinical risk to the subject
- All adverse events that meet discontinuation criteria, as well as any Grade 3 or 4 infusion reactions must be reported to BMS, within 24 hours using the rapid notification procedures described in Section 6.1.1.

Subjects who experience AEs that require discontinuation while receiving both nivolumab and ipilimumab may be allowed to continue therapy with nivolumab only if deemed in their best interest by both the PI and the BMS medical monitor. This will be decided on a case by case basis and will require convincing evidence that the benefit outweighs the risk.

4.3.6 Criteria to Resume Treatment with Study Drug

Subjects may resume treatment with study drug when the drug-related AE(s) resolve(s) to Grade 1 or baseline value. Subjects must be re-treated within 6 weeks from the previous dose. For selected patients who are assessed to be deriving clinical benefit from treatment or for patients where resumption of therapy is delayed, re-initiation of therapy may be delayed even further on a case-by-case basis in consultation with the Sponsor.

In the case of endocrine-related AEs, hormone replacement therapy may be utilized to restore physiologic function and to permit retreatment with nivolumab. If this is not possible, the subject must be discontinued from study therapy.

4.3.7 Criteria to Enter Extension Period

At the completion of two years of therapy, those subjects that meet the following criteria may continue to receive nivolumab at the dose of 3mg/kg every 2 weeks (14 days):

- Subject demonstrates investigator-assessed clinical benefit as defined by stable disease, partial response, or complete response
- Subjects who demonstrate a complete response can only receive treatment until confirmation of CR or for an additional 2 doses (whichever is longer) and then enter the follow up period.
- Subject is tolerating nivolumab therapy

All decisions to continue treatment in the Extension Period must be discussed with and approved by the BMS Medical Monitor and documented in the study records.

4.3.8 Treatment Beyond Progression of Disease

As described in Section 1.1.9, accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[76]

Subjects will be permitted to continue study drug beyond initial RECIST1.1 defined PD as long as they meet the following criteria:

- Continue to meet all other study protocol eligibility criteria
- Obtaining Investigator assessed clinical benefit and without rapid disease progression or clinical deterioration
- Stable performance status
- Tolerance of study drug
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)

A follow up scan should be performed at the next assessment or earlier 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 study drug. If the investigator feels that the subject continues to achieve clinical benefit by continuing treatment, the subjects should remain on trial and continue to receive monitoring according to the Time and Events Schedule on Tables in Section 5.1. The decision to continue treatment should be discussed with the BMS Medical Monitor and documented in the study records.

For the subjects who continue study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden volume from time of initial PD. This includes an increase in all target lesions and/or the development of new measurable lesions.

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

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

4.3.9 Infusion Delays and Missed Doses

In the case that an infusion cannot be administered at a scheduled visit, it should be administered as soon as possible. If the delay is between 1 and 7 days, the procedures at the original scheduled

visit should be performed. If the delay is more than 7 days, the infusion at the original scheduled visit will be considered a missed dose, and the procedures at the next visit should be performed. Response assessments must never be omitted. Subsequent visits will follow accordingly from the actual date of last study drug administration. Subjects with infusion delays ≥ 8 weeks should normally discontinue treatment and enter the follow-up period with the exception of delays as described in Section 4.3.6 and after specific consultation and agreement between the investigator and BMS Medical Monitor in settings where benefit/risk may justify continued study therapy.

4.3.10 Discontinuation Due to Confirmed Complete Response

Subjects with a CR may continue to receive study therapy until response confirmation or for an additional 2 cycles (whichever is longer) and then enter the follow-up period.

4.3.11 Stopping Rules for Clinical Deterioration

Accumulating evidence indicates that the emergence of objective responses to agents that activate anti-tumor immune responses may follow delayed kinetics of weeks or months, and can be preceded by initial apparent radiological progression or appearance of new lesions or some enlarging lesions while certain target lesions are regressing ("mixed response"). It is thus reasonable to allow for these possibilities and continue to treat the subject until progression is confirmed and found to be advancing and continuing at the next imaging assessment. These considerations should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment. Such deterioration will be assessed to have occurred after a clinical event that, in the Investigator's opinion, is attributable to disease progression, is unlikely to reverse with continued study treatment and therefore indicates that the subject is not benefiting from study treatment and cannot be managed by the addition of supportive care (such as bone directed radiotherapy, thoracentesis or paracentesis of accumulating effusions). The decision to continue or stop treatment should be discussed with the BMS Medical Monitor and will be documented in the study records.

4.3.12 Prophylactic and Acute Management of Infusion Reactions

Infusion reactions should be graded according to CTCAE Version 4.0 allergic reaction/hypersensitivity. These reactions may manifest with signs and symptoms that may include, but are not limited to fever, chills, headache, rash, pruritus, arthralgias, hypo-or hypertension, bronchospasm or other symptoms. Severe infusion reactions require the immediate interruption of study drug therapy and permanent discontinuation from further treatment. Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Subjects should be carefully observed until the complete resolution of all signs and symptoms. Following an infusion reaction, subjects should be premedicated with acetaminophen and diphenhydramine for future treatments.

Nivolumab and ipilimumab contain only human immunoglobulin protein sequences. Nevertheless, infusion reactions have been observed, although they are rare. If such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritis, arthralgias, hypotension or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion

reactions should be reported within 24 hours to the BMS Medical Monitor and reported as a SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE (version 4.0) guidelines.

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

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

The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional study drug administrations.

For Grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, 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 paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid 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. Monitor subject closely. If symptoms recur then no further study drug will be administered at that visit. Subsequent infusions should be administered over 2 hours. The amount of study drug infused must be recorded on the case report form (CRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional study drug administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of SoluCortef or equivalent) may be used.

For Grade 3 or Grade 4 symptoms: (Severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]. Grade 4: life-threatening; pressor or ventilatory support indicated). Immediately discontinue infusion of 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 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. 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 from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized

pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

4.3.13 *Guidelines for Management of Gastrointestinal, Pulmonary and Endocrine Adverse Events*

All subjects who receive treatment on this study should be closely monitored for any signs related to gastrointestinal, pulmonary or endocrine systems and aggressively managed at the first onset of clinical symptoms. A high index of suspicion for colitis, endocrinopathy (e.g. hypothyroidism or adrenal insufficiency) or pneumonitis should be maintained in all subjects who present with any symptoms referable to these events, including but not limited to diarrhea, abdominal symptoms, fatigue, lethargy, weakness, dehydration or shortness of breath. Prompt initiation of appropriate diagnosis and therapy, including early administration of steroids, should be instituted. Guidance is provided in the appendix of the Nivolumab Investigator Brochure[48] and Appendix 4.

4.4 Blinding/Unblinding

Not applicable for this study.

4.5 Treatment Compliance

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

4.6 Destruction and Return of Study Drug

4.6.1 *Destruction of Study Drug*

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

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

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

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

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

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

4.6.2 Return of Study Drug

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

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

4.7 Retained Samples for Bioavailability / Bioequivalence

Not applicable

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1A: CA209038 Screening Procedural Outline

Procedure	Screening Visit	Visit 1 Day -3 to Day 1	Notes
Eligibility Assessments			
Informed Consent	X		A subject is considered enrolled only when a protocol-specific informed consent is signed
Inclusion/Exclusion Criteria	X		All inclusion/exclusion criteria should be assessed prior to study assignment
Medical History	X		Include all previous treatments, any toxicities or allergy related to previous treatments, history of tobacco use (how many packs for how many years) and other pulmonary history (e.g. asthma or toxic exposures)
BRAF mutation status	X		A hard copy of BRAF mutation status must be made available to the investigator and the Sponsor. For Part 1 only: If BRAF status is not known, then subjects' archival tumor tissue will be sent for centralized testing at a Sponsor-selected lab. Fresh tumor tissue should be used for BRAF mutation status **only if** the BRAF status is unknown, no archival tumor tissue is available and if there is adequate tumor tissue for all other tumor tissue assays.
Tumor tissue samples	X		For Part 1, must have lesions from which a minimum of 2 core biopsies for FFPE and RNA extraction can be taken. For Part 2 and 3, excisional/incisional biopsies preferred from non-lymph node lesion and tumor tissue samples will be centrally assessed for sufficient tumor content (≧100 tumor cells/4-micon section); subjects with samples that have insufficient tumor content will require re-biopsy prior to treatment. In Part 4, pre-treatment and on-treatment biopsies are optional; although strongly recommended if clinically safe. For Parts 1-4, archival tissue (FFPE block or a minimum of 10 unstained slides) should be obtained if available. See Section 5.6 for detail.
Blood Samples for Biomarkers	X		See Table 5.5A or Table 5.5Band Laboratory Manual for more details

Table 5.1A: CA209038 Screening Procedural Outline			
Procedure	**Screening Visit**	**Visit 1 Day -3 to Day 1**	**Notes**
Disease Assessments	X		CT chest, CT or MRI abdomen and pelvis, as well as MRI of brain should be performed if not performed within 28 days of anticipated drug administration.
Safety Assessments			
Assessment of Signs and Symptoms	X		Within 2 weeks prior to treatment; Record all medications taken within the prior 28 days as per Section 3.4
Concomitant Med Collection	X		Within 2 weeks prior to treatment; Record all medications taken within the prior 28 days as per Section 3.4
Physical Examination	X		To include height, weight
Vital Signs (including ECOG Performance Status)	X	X	Includes body temperature, respiratory rate, seated blood pressure and heart rate. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes
Pulse oximetry	X		Collected at rest for at least 5 minutes. Oxygen levels will be used in combination with clinical signs and symptoms and radiographic images to evaluate pulmonary/respiratory status. Changes in O_2 levels will not used in isolation to document or diagnosis pulmonary toxicity
ECG	X		Single 12 lead measurement should be recorded after the subject has been supine for at least 5 minutes
Chest Radiograph	X		Unless performed within 30 days of anticipated first dose

Table 5.1A: CA209038 Screening Procedural Outline			
Procedure	**Screening Visit**	**Visit 1 Day -3 to Day 1**	**Notes**
Laboratory Tests (perform between day -14 to day -3)	X		To include CBC with differential, Complete Metabolic Panel (Na, K, Cl, CO_2, BUN or serum urea level, Cr, eGFR, AST, ALT, Alk Phos, Albumin, Total Bilirubin, Total Protein, Calcium, glucose), direct bilirubin, amylase, lipase, magnesium, phosphorous, LDH, TSH (with reflex to free T3 and free T4 if abnormal), adenocorticotropic hormone (ACTH) collected in the morning (with reflex to cortisol if abnormal), Hep B surface Ag, Hep C antibody, HIV 1/2 antibody (may obtain additional testing or substitute testing per institutional guidelines to rule out infections), and urinalysis (dipstick); Subjects with suspected autoimmune thyroid disorders will also be tested for thyroid peroxidase antibodies and thyroid stimulating immunoglobulin
Serum or Urine Pregnancy Test	X		For WOCBP within 24 hours of Study Drug Administration
Follicle Stimulating Hormone (FSH) test (perform between day -14 to day -3)	X		Only required in certain instances in post-menopausal women. See Section 3.3.3 for criteria
Adverse Event Reporting			
Monitor for Serious Adverse Events	X	X	All SAEs must be collected from the date of the subject's written consent until 100 days post discontinuation of dosing or subject's participation in the study if the last scheduled visit occurs at a later time

Table 5.1B: CA209038 Treatment Procedural Outline, Part 1 (Cohorts 1 and 2)						
Procedure	**Treatment Cycle = IV infusion q 2 weeks for 8 weeks**				**End of Treatment Visit**	**Notes**
	Day 1	**Day 15**	**Day 29**	**Day 43**		
Safety Assessments						
Physical Examination	X	X	X	X	X	Done weekly in Cycle 1; to include body weight
Vital Signs (including ECOG Performance status)	X	X	X	X	X	Measured before and after study drug administration. Includes body temperature, respiratory rate, seated blood pressure and heart rate. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes. Done weekly in Cycle 1 only.
Pulse oximetry	X	X	X	X	X	Collected at rest for at least 5 minutes, before each study drug administration. Oxygen levels will be used in combination with clinical signs and symptoms and radiographic images to evaluate pulmonary/respiratory status. Changes in O_2 levels will not be used in isolation to document or diagnosis pulmonary toxicity.
Monitor for Adverse Events	X	X	X	X	X	All **Non-Serious Adverse Events** will be collected from Day1 until the subject's 100 days post discontinuation of dosing or subject's participation in the study if the last scheduled visit occurs at a later time All **Serious Adverse Events** must be collected from the date of the subject's written consent until 100 days post discontinuation of dosing or subject's participation in the study if the last scheduled visit occurs at a later time
Review Concomitant medications	X	X	X	X	X	
Laboratory Tests	X	X	X	X	X	To include CBC with differential, Complete Metabolic Panel (Na, K, Cl, CO_2, BUN, Cr, eGFR, AST, ALT, Alk Phos, Albumin, Total Bilirubin, Total Protein, Calcium, glucose), direct bilirubin, lipase, LDH, magnesium, phosphorus

Table 5.1B:	CA209038 Treatment Procedural Outline, Part 1 (Cohorts 1 and 2)					
Procedure	**Treatment Cycle = IV infusion q 2 weeks for 8 weeks**				**End of Treatment Visit**	**Notes**
	Day 1	**Day 15**	**Day 29**	**Day 43**		
ECG	X				X	Single 12-lead ECGs will be collected at screening and prior to dosing on Day 1 of every other treatment cycle starting with Cycle 1. On Day 1 of Cycles 1, 2, and 4, an End of Infusion (EOI) ECG will be collected, as well. **Electrocardiogram recording should be obtained just prior to as the serial PK samples as indicated in Table 5.5A.**
Chest radiograph						As clinically indicated
Serum or Urine Pregnancy Test	X		X		X	Starting with Day 1 and then every other dose or every 28 days. For WOCBP within 24 hours of Study Drug Administration
Serum TSH	X					On Day 1 of each cycle
Exploratory						
Blood samples for PK, ADA, Biomarkers	See Table 5.5A for timing of samples					
Efficacy Response Assessments						
Disease assessment, Tumor Imaging (CT or MRI of Chest/Abdomen/Pelvis; MRI brain if clinically indicated				X (between days 49-56)	X	Tumor assessments should be done every 8 wks (+/- 1 wk) until confirmed disease progression is documented or follow-up is completed. **Methods used at baseline should be continued throughout study.** MRI of brain are only required if clinically indicated
Clinical Drug						
Dispense Study Drug/Treatment	X	X	X	X		Nivolumab will be administered as an IV infusion on Days 1, 15, 29, 43 of each 56 day treatment cycle (8 weeks/cycle)

Table 5.1C: CA209038 Follow-up Visits - Part 1 (Cohorts 1 and 2)		
Procedure	**Follow-up Visit 1 (40-60 days) and Visit 2 (101-120 days)**	**Notes**
Safety Assessments		
Physical Examination	X	
Vital Signs (including ECOG)	X	Includes body temperature, respiratory rate, pulse oximetry, seated blood pressure and heart rate. Blood pressure, pulse oximetry and heart rate should be measured after the subject has been seated quietly for at least 5 minutes
Adverse Events Assessment	X	For study related adverse events only
Review Concomitant Medications	X	
Laboratory Tests	X	To include CBC with differential, Complete Metabolic Panel (Na, K, Cl, CO_2, BUN, Cr, eGFR, AST, ALT, Alk Phos, Albumin, Total Bilirubin, Total Protein, Calcium, glucose), direct bilirubin, lipase, LDH, magnesium, phosphorus, TSH
Serum or Urine Pregnancy Test	X	
ECG	X	12 Lead; for the first two follow-up visits only. Measurement should be recorded after the subject has been supine for at least 5 minutes
Tumor biopsy	X (encouraged, not mandated)	Upon confirmed progression May be done at either Follow-up visit 1 or Follow-up visit 2

Table 5.1C: CA209038 Follow-up Visits - Part 1 (Cohorts 1 and 2)		
Procedure	**Follow-up Visit 1 (40-60 days) and Visit 2 (101-120 days)**	**Notes**
Efficacy Assessments		
Disease assessment (CT/MRI)	X	Done after 12 weeks from the last on-study scan during Follow-up Visit 1 OR 2 then Q12wks **by methods used at baseline** Not required for subjects entering follow-up period for confirmed disease progression
Exploratory		
Blood samples for PK, ADA	X	As per Table 5.5A
Survival Status	X	Survival status should be continued every 3 months for the time remaining after the last office follow-up visit until 2 years from the first dose of BMS-936558 or until subject death, subject withdraws consent, subject is lost-to follow-up or the study is completed. This may be accomplished by visit or phone contact.

Table 5.1D: On Treatment Procedural Outline (CA209038) - Part 2, Part 3 and Part 4: Arms A and D								
[Procedure Window ± 2 days]								
Procedure	**Wk1 Day 1**	**Wk4 Day 1**	**Wk7 Day 1**	**Wk10 Day 1**	**Wk 13 Day 1 and every 2 weeks thereafter**	**End of Therapy**	**Follow-Up Visits 1 and 2[a]**	**Notes**
Safety Assessments								
Targeted Physical Examination	X	X	X	X	X	X	X	To be performed only as clinically indicated
Vital Signs and Oxygen Saturation	X	X	X	X	X	X	X	Including BP, HR, temperature and oxygen saturation by pulse oximetry. Pulse oximetry at rest and after exertion within 72 hours prior to dosing
Physical Measurements (including performance status)	X	X	X	X	X	X	X	Weight and ECOG performance status
Adverse Events Assessment	X	X	X	X	X	X	X	Continuously throughout the study
Review of Concomitant Medications	X	X	X	X	X	X	X	
12 Lead ECG					X*			*To be performed pre-dose at Week 13, Week 23 and then every 16 weeks thereafter

Table 5.1D: On Treatment Procedural Outline (CA209038) - Part 2, Part 3 and Part 4: Arms A and D									
[Procedure Window ± 2 days]									
Procedure	**Wk1 Day 1**	**Wk4 Day 1**	**Wk7 Day 1**	**Wk10 Day 1**	**Wk 13 Day 1 and every 2 weeks thereafter**	**End of Therapy**	**Follow-Up Visits 1 and 2[a]**	**Notes**	
Laboratory Tests									
Serum Chemistry	X	X	X	X	X		X	X	Within 72 hours prior to re-dosing to include:, Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, lactate dehydrogenase, creatinine, blood urea nitrogen (BUN) or serum urea level, amylase, lipase, glucose, sodium, potassium, chloride, CO_2 calcium, magnesium, TSH (if TSH is abnormal then obtain free T3 and free T4), ACTH collected in the morning as clinically indicated.
Hematology	X	X	X	X	X		X	X	Within 72 hours prior to re-dosing to include CBC with differential NOTE: Additionally required for the PBMC sample collection at the following timepoints: Week 1 Day 4; Week 2 Day 1; Week 3 Day 1; and Week 5 Day 1
Pregnancy Test (WOCBP only)	X	X	X	X	X	X	X	X	Serum or urine within 24 hours prior to administration of study drug

Table 5.1D: On Treatment Procedural Outline (CA209038) - Part 2, Part 3 and Part 4: Arms A and D									
[Procedure Window ± 2 days]									
Procedure	**Wk1 Day 1**	**Wk4 Day 1**	**Wk7 Day 1**	**Wk10 Day 1**	**Wk 13 Day 1 and every 2 weeks thereafter**	**End of Therapy**	**Follow-Up Visits 1 and 2[a]**	**Notes**	
Pharmacokinetic Samples									
PK samples									See Table 5.5C or Table 5.5E for schedule of samples
Other Samples									
Immunogenicity blood sample (ADA)									See Table 5.5C or Table 5.5E for schedule of samples
Biomarker Samples									See Table 5.5B for schedule of samples
Efficacy Assessment									
Tumor Assessment			X		X			Subsequent assessments at week 23, then every 8 weeks thereafter. May be obtained up to 7 days prior to the required visit. CT Chest and CT or MRI abdomen, pelvis and all known sites of disease. Use same imaging method used at screening. Arm D only, MRI brain also (subjects in other arms who have stable brain metastases should have surveillance brain MRI approximately every 16 weeks and as clinically indicated).	

Table 5.1D: On Treatment Procedural Outline (CA209038) - Part 2, Part 3 and Part 4: Arms A and D								
[Procedure Window ± 2 days]								
Procedure	**Wk1 Day 1**	**Wk4 Day 1**	**Wk7 Day 1**	**Wk10 Day 1**	**Wk 13 Day 1 and every 2 weeks thereafter**	**End of Therapy**	**Follow-Up Visits 1 and 2[a]**	**Notes**
Survival Data Collection							X	Survival status should be continued every 3 months for the time remaining after the last office follow-up visit until 2 years from the first dose of study drug or until subject death, subject withdraws consent, subject is lost-to follow-up or the study is completed. This may be accomplished by visit or phone contact.
Clinical Drug Supplies								
IVRS drug vial assignment	X	X	X	X	X			
Nivolumab Infusion treatment	X	X	X	X	X			
Ipilimumab Infusion treatment	X	X	X	X				

[a] Follow up Visit 1 and 2 will occur at 40-60 days and 101-120 days after the stop of study therapy, respectively. Efficacy is required at Follow up visit 2 only.

Table 5.1E: On Treatment Procedural Outline (CA209038) - Part 3 and Part 4: Arms B and E [a]				
[Procedure Window ± 2 days]				
Procedure	**Wk1 Day 1 and every 2 weeks thereafter**	**End of Therapy**	**Follow-Up Visits 1 and 2 [b]**	**Notes**
Safety Assessments				
Targeted Physical Examination	X	X	X	To be performed only as clinically indicated
Vital Signs and Oxygen Saturation	X	X	X	Including BP, HR, temperature and oxygen saturation by pulse oximetry. Pulse oximetry at rest and after exertion within 72 hours prior to dosing
Physical Measurements (including performance status)	X	X	X	Weight and ECOG performance status
Adverse Events Assessment	X	X	X	Continuously throughout the study
Review of Concomitant Medications	X	X	X	
12 Lead ECG	See note			To be performed pre-dose at week 13, week 23 and then every 16 weeks thereafter
Laboratory Tests				
Serum Chemistry	X	X	X	Within 72 hours prior to re-dosing to include:, Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, lactate dehydrogenase, creatinine, blood urea nitrogen (BUN) or serum urea level, amylase, lipase, glucose, sodium, potassium, chloride, CO_2, calcium, magnesium, TSH (if TSH is abnormal then obtain free T3 and free T4), ACTH collected in the morning as clinically indicated.
Hematology	X	X	X	Within 72 hours prior to re-dosing to include CBC with differential NOTE: Additionally required for the PBMC sample collection at the following timepoints: Week 1 Day 4; Week 2 Day 1; and Week 4 Day 1

Table 5.1E: On Treatment Procedural Outline (CA209038) - Part 3 and Part 4: Arms B and E [a]				
[Procedure Window ± 2 days]				
Procedure	**Wk1 Day 1 and every 2 weeks thereafter**	**End of Therapy**	**Follow-Up Visits 1 and 2[b]**	**Notes**
Pregnancy Test (WOCBP only)	X	X	X	Serum or urine within 24 hours prior to administration of study drug
Pharmacokinetic Samples				
PK samples				See Table 5.5D for schedule of samples
Other Samples				
Immunogenicity blood sample (ADA)				See Table 5.5D for schedule of samples
Biomarker Samples				See Table 5.5B for schedule of samples
Efficacy Assessment				
Tumor Assessment	See Note			Assessments at week 7, 13, 23 and then every 8 weeks thereafter. May be obtained up to 7 days prior to the required visit. CT Chest and CT or MRI abdomen, pelvis and all known sites of disease. Use same imaging method used at screening. Arm E only, MRI brain also (subjects in other arms who have stable brain metastases should have surveillance brain MRI approximately every 16 weeks and as clinically indicated).
Survival Data Collection			X	Survival status should be continued every 3 months for the time remaining after the last office follow-up visit until 2 years from the first dose of study drug or until subject death, subject withdraws consent, subject is lost-to follow-up or the study is completed. This may be accomplished by visit or phone contact.
Clinical Drug Supplies				
IVRS drug vial assignment	X			
Nivolumab Infusion treatment	X			

[a] Treatment Procedural Outline for subjects who progressed on Arm C.

[b] Follow up Visit 1 and 2 will occur at 40-60 days and 101-120 days after the stop of study therapy, respectively. Efficacy is required at Follow up visit 2 only.

Table 5.1F: On Treatment Procedural Outline (CA209038) - Part 2, Part 3 and Part 4: Arms A, B, D, and E				
[Procedure Window ± 2 days]				
Procedure	**Extension Period Starting at 2 years Every 2 weeks +/- 2 days**	**End of Therapy**	**Follow-Up Visits 1 and 2[a]**	**Notes**
Safety Assessments				
Targeted Physical Examination	X	X	X	To be performed only as clinically indicated
Vital Signs and Oxygen Saturation	X	X	X	Including BP, HR, temperature and oxygen saturation by pulse oximetry. Pulse oximetry at rest and after exertion within 72 hours prior to dosing
Physical Measurements (including performance status)	X	X	X	Weight and ECOG performance status
Adverse Events Assessment	X	X	X	Continuously throughout the study
Review of Concomitant Medications	X	X	X	Continuously throughout the study
12 Lead ECG	See note			To be performed every 16 weeks thereafter
Laboratory Tests				
Serum Chemistry	X	X	X	Within 72 hours prior to re-dosing to include:, Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, lactate dehydrogenase, creatinine, blood urea nitrogen (BUN) or serum urea level, amylase, lipase, glucose, sodium, potassium, chloride, CO_2, calcium, magnesium, TSH (if TSH is abnormal then obtain free T3 and free T4), ACTH collected in the morning as clinically indicated.
Hematology	X	X	X	Within 72 hours prior to re-dosing to include CBC with differential
Pregnancy Test (WOCBP only)	X	X	X	Serum or urine within 24 hours prior to administration of study drug
Efficacy Assessment				
Tumor Assessment	X	X	X	Subsequent assessments at week 23, then every 8 weeks thereafter.

Table 5.1F: On Treatment Procedural Outline (CA209038) - Part 2, Part 3 and Part 4: Arms A, B, D, and E				
[Procedure Window ± 2 days]				
Procedure	**Extension Period Starting at 2 years** **Every 2 weeks +/- 2 days**	**End of Therapy**	**Follow-Up Visits 1 and 2[a]**	**Notes**
				May be obtained up to 7 days prior to the required visit. CT Chest and CT or MRI abdomen, pelvis and all known sites of disease. Use same imaging method used at screening. Arms D and E only, MRI brain also (subjects in other arms who have stable brain metastases should have surveillance brain MRI approximately every 16 weeks and as clinically indicated).
Survival Data Collection			X	Patients that enter the Extension Period will be followed for overall survival assessments up to a maximum of 100 days after the last treatment dose.
Clinical Drug Supplies				
IVRS drug vial assignment	X			
Nivolumab Infusion treatment	X			

[a] Follow up Visit 1 and 2 will occur at 40-60 days and 101-120 days after the stop of study therapy, respectively. Efficacy is required at Follow up visit 2 only.

5.2 Study Materials

The following materials will be provided at study start:

- Protocol and appendices;
- NCI CTCAE version 4.0;
- Nivolumab Investigator Brochure;
- Ipilimumab Investigator Brochure;
- Laboratory kits, shipping materials;
- Laboratory manuals for collection and handling of blood (including PKs, biomarker and immunogenicity) and tissue specimens;
- Enrollment/randomization worksheets;
- Pregnancy Surveillance Forms;
- SAE reporting instructions and forms.

5.3 Safety Assessments

At baseline, a medical history will be obtained to capture relevant underlying conditions. Baseline signs and symptoms are those that are assessed within 2 weeks prior to treatment arm assignment. The baseline physical examination should include: weight, height, ECOG performance status, blood pressure, heart rate, electrocardiogram, O_2 saturation (pulse oximetry) and temperature; it should be performed within 28 days of treatment arm assignment. Concomitant medications will be collected from within 2 weeks prior to treatment arm assignment through the study treatment period (see Table 5.1A, Table 5.1B, Table 5.1C, Table 5.1D, and Table 5.1E).

Subjects will be considered evaluable for safety if they have received any study drug.

Toxicity assessments will be continuous during the treatment phase and follow-up phases.

Performance status and body weight should be assessed at each on study visit. Vital signs should also be taken as per institutional standard of care prior to, during and after the infusions with investigational products. Pulse oximetry should be done prior to each infusion as well. The start and stop time of the study drug infusion should be documented. If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate non-serious or serious adverse event page.

Additional measures including non-study required laboratory tests should be performed as clinically indicated.

Safety assessments will be based on the medical review of adverse event reports, results of vital sign measurements, Eastern Cooperative Oncology Group (ECOG) performance status, physical examinations, clinical laboratory results, ECGs, and imaging tests.

The incidence of observed adverse events will be categorized using the most current version of MedDRA and reviewed for potential significance and clinical importance. Adverse events will

be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.

5.3.1 Laboratory Test Assessments

Clinical laboratories will be assessed (see Table 5.1A, Table 5.1B, Table 5.1C, Table 5.1D, and Table 5.1E). Sites should collect screening samples between -14 to -3 days from assignment to insure that results required for eligibility purposes are verified prior to the assignment to study. Estimated GFR will be calculated by either Cockroft-Gault, CKD-EPI, or MDRD, formulas from the supplied serum creatinine value supplied by the site. Pregnancy testing must be performed within 24 hours prior to the initial administration of investigational product at baseline and then within 24 hours of each study drug administration. CBC plus differential and serum chemistry panel should be drawn within 72 hours prior to each subsequent scheduled treatment. On study labs will be done on site/locally. Laboratory tests may be done more frequently if indicated. Additional laboratory tests should be performed as per standard of care.

Laboratory toxicities (eg, suspected drug induced liver enzyme elevations) 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.

The following clinical laboratory tests will be performed:

Hematology

WBC
Hemoglobin
Hematocrit
MCV
RDW
Differential Count
Platelet count

Serum Chemistry

Sodium
Potassium
Chloride
CO_2
Blood Urea Nitrogen (BUN) or serum urea level
Creatinine
Estimated GFR
Glucose
Calcium
Magnesium
Phosphorus
Aspartate Transaminase
Alanine Transaminase
Alkaline Phosphatase
Total Bilirubin

Direct Bilirubin
Albumin
Total Protein
Amylase
Lipase
Lactate Dehydrogenase

Serology (screening only)

Human immunodeficiency virus 1/2 antibody
Hepatitis B virus surface antigen
Hepatitis C antibody

Note: May obtain additional testing or substitute testing per institutional guidelines to rule out infection

Urine Studies (screening only)

Urinalysis (dipstick)

Other Assays

TSH (if TSH is abnormal then obtain free T3 and free T4)
Anti- thyroid antibodies (stimulating and anti-thyroperoxidase (TPO) at screening only)
Adenocorticotropic hormone collected in the morning at screening, then as clinically indicated (if ACTH is abnormal then obtain cortisol)

Other Analyses

Pregnancy test (WOCBP only at screening and 24hrs prior study drug administration
FSH (if needed to document post-menopausal status as defined in Section 3.3.3)

At the investigator's discretion, laboratory tests may be repeated if clinically significant.

Results of all laboratory tests required by this protocol must be provided to BMS, either recorded on the laboratory pages of the CRF or by another mechanism as agreed upon between the investigator and BMS (eg, provided electronically). If the units of a test result differ from those printed on the CRF, the recorded laboratory values must specify the correct units. Any abnormal laboratory test result considered clinically significant by the investigator must be recorded on the appropriate AE page of the CRF (see Section 6.2 Laboratory Test Abnormalities).

5.3.2 ECG Evaluation

Single 12-lead ECGs will be collected at screening and on study.

5.4 Efficacy Assessments

Disease evaluation with computed tomography (CT) and/or magnetic resonance imaging (MRI) of chest, abdomen, and pelvis, as appropriate, will be performed at baseline, and then

approximately every 8 weeks until confirmed disease progression as described in Section 4.3.8 and/or completion of follow-up. Brain MRI will be performed at screening, approximately every 16 weeks thereafter, and if clinically indicated. Brain MRI will be performed approximately every 8 weeks for subjects in Arms D and E.

In the Extension Period, tumor assessments will be performed every 8 weeks (prior to dosing). CT Chest and CT or MRI abdomen, pelvis and all known sites of disease should be performed using the same imaging method used at screening. For Arms D and E only, MRI brain will also be performed (subjects in other arms who have stable brain metastases should have surveillance brain MRI approximately every 16 weeks and as clinically indicated).

Tumor response will be determined for all subjects as defined by RECIST 1.1. Individual patients will be treated according to principles that allow treatment beyond initial radiographic progression (outlined in Section 4.3.8).

At the sponsor's discretion, scans and measurements may be reviewed by independent radiologists using RECIST 1.1 criteria at a later date or any time during the study. In the absence of clinical deterioration, any initial assessment of progressive disease (PD) will be confirmed by a repeat evaluation at the next tumor assessment time point, but no sooner than 4 weeks later.

5.5 Pharmacokinetic Assessments

Table 5.5A, Table 5.5C, Table 5.5D and Table 5.5E list the sampling schedule to be followed for the assessment of pharmacokinetics. 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, and end-of-infusion (EOI) samples should be taken as close to EOI as possible (preferably 2 minutes prior to EOI) on the contralateral arm (ie, the arm not for the infusion). **All other on-treatment timepoints are relative to the start of study drug administration; when both nivolumab and ipilimumab are administered on the same day, samples should be collected relative to the start of nivolumab infusion**. If the infusion was interrupted, the reason for interruption should also be documented on the CRF. Blood samples will be processed to collect serum. PK samples will be analyzed for nivolumab or ipilimumab by validated immunoassays. Additional exploratory analysis may be conducted; exploratory results will not be reported. Further details of blood collection, labeling, processing, storage and shipping will be provided to the site in the laboratory manual.

Table 5.5A: CA209038 Pharmacokinetic (PK), Pharmacodynamic, and Biomarker Sampling Schedule (Part 1, Cohorts 1 and 2)

Study Day	Time (Event)	Time (Relative to Start of Infusion) Hours:Min	PK Serum Sample	ADA	SNP& HLA/ KIR typing	Tumor Ag specific T-cells with a CBC and differential	PB Gene Expression Profiling	PBMC Flow Cytometry with a CBC and differential	Soluble Factors (Serum)	Anti-Tumor Antibodies	PBMC Functional Assays with a CBC and differential	Tumor Biopsy
Screening (day -7 to day1 pre-dose)					X	X	X	X	X	X	X	X (once eligibility determined)
Cycle1 Day 1	0 (predose)	00:00	X	X			X					
Cycle1 Day 1	1 (EOI)	01:00	X									
Cycle1 Day 1	3	03:00	X						X			
Cycle1 Day 1	7	07:00	X						X			
Cycle 1 Day 2	0	24:00	X				X		X			
Cycle 1 Day 3	0	48:00	X									
Cycle 1 Day 4	0	72:00	X					X[a]				
Cycle 1 Day 8	0	168:00	X				X	X[a]			X[a]	

Table 5.5A: CA209038 Pharmacokinetic (PK), Pharmacodynamic, and Biomarker Sampling Schedule (Part 1, Cohorts 1 and 2)

Study Day	Time (Event)	Time (Relative to Start of Infusion) Hours:Min	PK Serum Sample	ADA	SNP& HLA/ KIR typing	Tumor Ag specific T-cells with a CBC and differential	PB Gene Expression Profiling	PBMC Flow Cytometry with a CBC and differential	Soluble Factors (Serum)	Anti-Tumor Antibodies	PBMC Functional Assays with a CBC and differential	Tumor Biopsy
Cycle1 Day 15	0 (predose)	00:00	X	X				X	X		X	
Cycle 1 Day 29	0 (predose)	00:00	X			X	X	X	X	X	X	X (day 23 to day 29)
Cycle 1 Day 43	0 (predose)	00:00	X	X					X			
Cycle 1 Day 43	1 (EOI)	01:00	X									
Cycle2 Day1	0 (predose)	00:00	X	X		X	X	X		X	X	
Cycle 2 Day 29	0 (predose)	00:00	X									
Cycle 3 Day 15	0 (predose)	00:00	X	X								
Cycle 3 Day 15	1 (EOI)	01:00	X									
Cycle 5 Day 1 (Every 16 weeks after Cycle 3)	0 (predose)	00:00	X	X								

Table 5.5A: CA209038 Pharmacokinetic (PK), Pharmacodynamic, and Biomarker Sampling Schedule (Part 1, Cohorts 1 and 2)

Study Day	Time (Event)	Time (Relative to Start of Infusion) Hours:Min	PK Serum Sample	ADA	SNP& HLA/ KIR typing	Tumor Ag specific T-cells with a CBC and differential	PB Gene Expression Profiling	PBMC Flow Cytometry with a CBC and differential	Soluble Factors (Serum)	Anti-Tumor Antibodies	PBMC Functional Assays with a CBC and differential	Tumor Biopsy
Follow-up Visit 1 (40-60 days after last treatment			X	X								
Follow-up Visit 2 (101-120 days since last treatment)			X	X								

[a] CBCs required will be done locally and not by central lab

Table 5.5B: CA209038 Pharmacodynamic and Biomarker Sampling Schedule (Parts 2, 3 and 4, Arms A, B, D and E)

Study Day	Time (Event)	Time (Relative to Start of Infusion) Hours:Min	SNP& HLA/ KIR typing	Tumor Ag specific T-cells with a CBC and differential	MDSCs	PB Gene Expression Profiling	PBMC Flow Cytometry with a CBC and differential	Soluble Factors (Serum)	Anti-Tumor Antibodies	PBMC Functional Assays with a CBC and differential	Tumor Biopsy
Screening			X	X[a]	X	X	X[a]	X	X	X[a]	X[b,c]
Week 1 Day 1	0 (predose)	00:00				X					
Week 1 Day 1	3 h	03:00						X			
Week 1 Day 1	7 h	07:00						X			
Week 1 Day 2	0	24:00				X		X			
Week 1 Day 3	0	48:00						X			
Week 1 Day 4	0	72:00					X[a]	X			
Week 2 Day 1	0	168:00				X	X[a]	X		X[a]	X (+7 days)[c,d]

Table 5.5B: CA209038 Pharmacodynamic and Biomarker Sampling Schedule (Parts 2, 3 and 4, Arms A, B, D and E)

Study Day	Time (Event)	Time (Relative to Start of Infusion) Hours:Min	SNP& HLA/ KIR typing	Tumor Ag specific T-cells with a CBC and differential	MDSCs	PB Gene Expression Profiling	PBMC Flow Cytometry with a CBC and differential	Soluble Factors (Serum)	Anti-Tumor Antibodies	PBMC Functional Assays with a CBC and differential	Tumor Biopsy
Week 3 Day 1	0 (predose)	00:00				X	X[a]	X		X[a]	
Week 4 Day 1	0 (predose)					X	X[a]	X		X[a]	X (+7 days after 2nd dose)[c,e]
Week 5 Day 1	0 (predose)	00:00		X[a]		X	X[a]	X		X[a]	
Week 7 Day 1	0 (predose)	00:00			X	X	X[a]	X	X	X[a]	
Week 13 Day 1	0 (predose)	00:00		X[a]			X[a]		X	X[a]	
Follow-up Visit 1 (40-60 days after last treatment											X - obtain upon progression[f]
Follow-up Visit 2 (101-120 days after last treatment)											X - obtain upon progression[f]

Table 5.5B: CA209038 Pharmacodynamic and Biomarker Sampling Schedule (Parts 2, 3 and 4, Arms A, B, D and E)

Study Day	Time (Event)	Time (Relative to Start of Infusion) Hours:Min	SNP& HLA/ KIR typing	Tumor Ag specific T-cells with a CBC and differential	MDSCs	PB Gene Expression Profiling	PBMC Flow Cytometry with a CBC and differential	Soluble Factors (Serum)	Anti-Tumor Antibodies	PBMC Functional Assays with a CBC and differential	Tumor Biopsy
Upon occurrence of ≥ Grade 3/4 drug-related AE								X			
Local surgery of isolated symptomatic lesions (see Section 3.4.1)											X[f]
Re-treatment after interrupted active treatment											X[f]

[a] CBCs required will be done locally and not by central lab

[b] Must contain sufficient tumor content (≥100 tumor cells in a 4 micron section) upon central pathology assessment;

[c] Biopsy is strongly encouraged but not mandatory in Part 4

[d] On-treatment biopsy window for Part 2, group 1 biopsy is Week 2, Day 1+7 days; potential on-treatment biopsy window for Parts 3 and 4, if determined to be optimal biopsy window.

[e] On-treatment biopsy window for Part 2, group 2 is Week 4, Day 1+7 days; potential on-treatment biopsy window for Parts 3 and 4, if determined to be optimal biopsy window.

[f] Biopsy is strongly encouraged but not mandatory. May be done at either Follow-up visit 1 or Follow-up visit 2

Table 5.5C: PK and ADA Sampling Schedule - Part 2 Arm A

Study Day	Time (Event)	Time (Relative to Start of Nivolumab Infusion) Hours Min[a]	PK Serum Sample Nivolumab	Immuogenicity Sample Nivolumab	PK Serum Sample Ipilimumab	Immunogenicity Sample Ipilimumab
Week 1 Day 1	0 (predose)	00:00	X	X	X	X
Week 1 Day 1	1 h (EOI-Nivo)	01:00	X			
Week 1 Day 1	3 h (EOI-Ipi)	03:00	X		X	
Week 1 Day 1		07:00	X		X	
Week 1 Day 2		24:00	X		X	
Week 1 Day 3		48:00	X		X	
Week 1 Day 4		72:00	X		X	
Week 2 Day 1		168:00	X		X	
Week 4 Day 1	0 (predose)	00:00	X	X	X	X
Week 7 Day 1	0 (predose)	00:00	X	X	X	X
Week 7 Day 1	1 h (EOI-Nivo)	01:00	X			
Week 7 Day 1	3 h (EOI-Ipi)	03:00			X	
Week 10 Day 1	0 (predose)	00:00	X	X	X	X
Week 13 Day 1	0 (predose)	00:00	X	X	X	
Week13 Day 1	1 h (EOI-Nivo)	01:00	X			
Week 25 Day 1	0 (predose)	00:00	X	X	X	X

Table 5.5C: PK and ADA Sampling Schedule - Part 2 Arm A

Study Day	Time (Event)	Time (Relative to Start of Nivolumab Infusion) Hours Min[a]	PK Serum Sample Nivolumab	Immuogenicity Sample Nivolumab	PK Serum Sample Ipilimumab	Immunogenicity Sample Ipilimumab
Week 53 Day 1	0 (predose)	00:00	X	X	X	X
Week 79 Day 1	0 (predose)	00:00	X	X		
Week 95 Day 1	0 (predose)	00:00	X	X		
Follow-up Visit 1 (40-60 days after last treatment)			X	X	X[b]	X[b]
Follow-up Visit 2 (101-120 days since last treatment)			X	X	X[b]	X[b]

[a] All samples should be timed relative to the **start of nivolumab** infusion, except for the ipilimumab end of infusion (EOI) samples which are to be taken just prior to the end of the ipilimumab infusion.

[b] Ipilimumab Follow up PK and immunogenicity samples collected only if subject discontinues treatment before Week 25.

Table 5.5D: PK and ADA Sampling Schedule Part 3 and Part 4, Arm B and E

Study Day	Time (Event)	Time (Relative to Start of Infusion) Hours:Min	PK Serum Sample Nivolumab	Immunogenicity Sample Nivolumab
Week 1 Day 1	0 (predose)	00:00	X	X
Week 1 Day 1	0.5 (EOI)	00:30	X	
Week 1 Day 1		03:00	X	
Week 1 Day 1		07:00	X	
Week 1 Day 2		24:00	X	
Week 1 Day 3		48:00	X	
Week 1 Day 4		72:00	X	
Week 2 Day 1		168:00	X	
Week 3 Day 1	0 (predose)	00:00	X	X
Week 5 Day 1	0 (predose)	00:00	X	
Week 7 Day 1	0 (predose)	00:00	X	X
Week 7 Day 1	0.5 h (EOI)	00:30	X	
Week 13 Day 1	0 (predose)	00:00	X	X
Week 13 Day 1	0.5 h (EOI)	00:30	X	
Week 25 Day 1	0 (predose)	00:00	X	X
Week 53 Day 1	0 (predose)	00:00	X	X
Week 79 Day 1	0 (predose)	00:00	X	X

Table 5.5D: PK and ADA Sampling Schedule Part 3 and Part 4, Arm B and E

Study Day	Time (Event)	Time (Relative to Start of Infusion) Hours:Min	PK Serum Sample Nivolumab	Immunogenicity Sample Nivolumab
Week 95 Day 1	0 (predose)	00:00	X	X
Follow-up Visit 1 (40-60 days after last treatment)			X	X
Follow-up Visit 2 (101-120 days since last treatment)			X	X

Table 5.5E: PK and ADA Sampling Schedule - Parts 3 and 4 Arm A and D

Study Day	Time (Event)	Time (Relative to Start of Nivolumab Infusion) Hours Min[a]	PK Serum Sample Nivolumab	Immuogenicity Sample Nivolumab	PK Serum Sample Ipilimumab	Immunogenicity Sample Ipilimumab
Week 1 Day 1	0 (predose)	00:00	X	X	X	X
Week 1 Day 1	0.5 h (EOI-Nivo)	00:30	X			
Week 1 Day 1	1.5 h (EOI-Ipi)	01:30	X		X	
Week 1 Day 1		07:00	X		X	
Week 1 Day 2		24:00	X		X	
Week 1 Day 3		48:00	X		X	
Week 1 Day 4		72:00	X		X	
Week 2 Day 1		168:00	X		X	
Week 4 Day 1	0 (predose)	00:00	X	X	X	X
Week 7 Day 1	0 (predose)	00:00	X	X	X	X
Week 7 Day 1	0.5 h (EOI-Nivo)	00:30	X			
Week 7 Day 1	1.5 h (EOI-Ipi)	01:30			X	
Week 10 Day 1	0 (predose)	00:00	X	X	X	X
Week 13 Day 1	0 (predose)	00:00	X	X	X	
Week13 Day 1	0.5 h (EOI-Nivo)	00:30	X			
Week 25 Day 1	0 (predose)	00:00	X	X	X	X

Table 5.5E: PK and ADA Sampling Schedule - Parts 3 and 4 Arm A and D

Study Day	Time (Event)	Time (Relative to Start of Nivolumab Infusion) Hours Min[a]	PK Serum Sample Nivolumab	Immuogenicity Sample Nivolumab	PK Serum Sample Ipilimumab	Immunogenicity Sample Ipilimumab
Week 53 Day 1	0 (predose)	00:00	X	X	X	X
Week 79 Day 1	0 (predose)	00:00	X	X		
Week 95 Day1	0 (predose)	00:00	X	X		
Follow-up Visit 1 (40-60 days after last treatment)			X	X	X[b]	X[b]
Follow-up Visit 2 (101-120 days since last treatment)			X	X	X[b]	X[b]

[a] All samples should be timed relative to the **start of nivolumab** infusion, except for the ipilimumab end of infusion (EOI) samples which are to be taken just prior to the end of the ipilimumab infusion.

[b] Ipilimumab Follow up PK and immunogenicity samples collected only if subject discontinues treatment before Week 25.

[redacted]

5.8 Outcomes Research Assessments

Not applicable for this study

[redacted]

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

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

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

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

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

An algorithm for the suggested management of drug-related immune events is included in Appendix of the Nivolumab Investigator Brochure.

6.1 Serious Adverse Events

A ***serious AE (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI).

Suspected transmission of an infectious agent (e.g., any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.4 for reporting pregnancies).

NOTE:

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

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

6.1.1 Serious Adverse Event Collection and 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, of any causality, must be collected that occur during the screening period and within 100 days of discontinuation of dosing for those subjects that receive study therapy (within 30 days of last visit for enrollment failures). If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy).

The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its status of 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 should 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 BMS (or designee) within 24 hours. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). When using paper forms, the reports are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: See Contact Information list.

SAE Facsimile Number: See Contact Information list.

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

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

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

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

All SAEs should be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

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

6.2.1 Nonserious Adverse Event Collection and Reporting

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.

In the event that a subject has a late emerging (after 100 days from last dose of study drug) non-laboratory, study drug related toxicity, it should be reported as an adverse event.

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, or those that are 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.

6.3 Laboratory Test Result Abnormalities

The following laboratory abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

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

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

6.4 Pregnancy

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

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

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

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

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 the Sponsor. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 Overdose

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

6.6 Potential Drug Induced Liver Injury (DILI)

Whenever 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:

ALT or AST elevation > 3 times upper limit of normal (ULN)

AND

Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

No other immediately apparent possible causes of aminotransferase 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, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the 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 for this study.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

The primary objective of this study is to assess the pharmacodynamic activity of immunomodulatory biomarkers following treatment with nivolumab and nivolumab in combination with ipilimumab. It is of interest to ensure precision of the estimate of the ratio of on-treatment biomarker assessments to baseline levels in Part 1 cohorts 1 and 2. Assuming that a biomarker is measured as a continuous variable, 40 subjects per cohort will provide the following confidence that the estimate of the ratio of on-treatment to baseline values will be within 20% of the true value:

Table 8.1A: Probability that estimated ratio of on-treatment to baseline value is within 20% of true value

Intra-subject Standard deviation (log-scale)	0.20	0.30	0.40	0.50	0.60	0.70	0.80
Probability	100%	100%	97%	93%	86%	80%	74%

For example, for a biomarker with an intra-subject standard deviation of 0.5, if the true ratio of post-baseline to baseline geometric means is 1.2 (increase from baseline is 20%), there is 93% probability that the estimated ratio would be within 0.96 and 1.44 (or a percent change between -4% and 44%). If the true increase from baseline is 60%, for a biomarker with the same variability, then there is 93% probability that the estimated percent change would be between 28% and 92%.

More specifically, preliminary data analysis of activated and memory CD4 and CD8 T cells in CA209003 project an intra-subject standard deviation on the log scale between 0.5 and 0.6. Assuming this variability estimate is applicable to this study, there is 86%-93% probability that the geometric mean ratio of on-treatment to baseline T cell subset levels will be within 20% of their true value.

It is of interest to ensure precision of the estimate of the proportion of subjects with increased activated T cells on-treatment (at optimal window for biopsy) in part 2 and part 3 Arms A and B. With a total of 30 subjects (from part 2 and part 3) treated in Arm A (with biopsy collected at optimal on-treatment window), the maximum width of the exact 2-sided 95% confidence interval (CI) is 37% when the proportion of subjects with increased activated T cells is expected to be in the 20% to 60% range. The 95% exact CIs are presented in Table 8.1B.

Table 8.1B: 95% Exact CI for Proportion of Subjects with Increased Activated T cell On-treatment

Proportion	20%	30%	40%	50%	60%
95% Exact CI	(7.7%, 38.6%)	(14.7%, 49.4%)	(22.7%, 59.4%)	(31.3%, 68.7%)	(40.6%, 77.3%)

With a total of 10 subjects treated in Arm B (with biopsy collected at optimal on-treatment window), the maximum width of the exact 2-sided 95% confidence interval (CI) is 59% when the proportion of subjects with increased activated T cells is expected to be in the 20% to 30% range. The 95% exact CIs are presented in Table 8.1C.

Table 8.1C: 95% Exact CI for Proportion of Subjects with Increased Activated T cell On-treatment

Proportion	20%	30%
95% Exact CI	(2.5%, 55.6%)	(6.7%, 65.3%)

For example, if the observed proportion of subjects with increased activated T cell is 20% (data from CA184-004 indicate that ~25% of metastatic melanoma patients have an intratumoral, activated T cells with ipilimumab alone), there is 95% probability that the exact CI (2.5%, 55.6%) will cover the true proportion.

Approximately 10 subjects will be treated in Arm D and 10 subjects in Arm E to provide additional information regarding pharmacodynamic activity of immunomodulatory biomarkers following treatment with nivolumab and nivolumab in combination with ipilimumab. Administration of nivolumab and nivolumab in combination with ipilimumab to 10 subjects per arm provides 90% probability of observing at least one occurrence of any adverse event (or one response) that would occur with a 21% incidence in the population from which the sample is drawn.

8.2 Populations for Analyses

- *All Enrolled Subjects*: All subjects who sign an informed consent form and were registered into the IVRS.
- *All Treated Subjects*: All subjects who receive at least one dose of study medication.
- *Pharmacokinetic Subjects*: All subjects who receive at least once dose of study medication and have available serum concentration data.
- *Response-Evaluable Subjects*: All treated subjects with measureable disease at baseline and one of the following: 1) at least one on-treatment tumor assessment, 2) clinical progression, or 3) death, if death occurred within 100 days after last administration of study medication

- *Immunogenicity Subjects*: All treated subjects who have baseline and at least one post baseline immunogenicity assessment
- *Biomarker Subjects*: All subjects who receive at least one dose of study medication and have available biomarker data

8.3 Endpoint Definitions

8.3.1 Primary Endpoints

The primary objective relating to the pharmacodynamic activity of biomarkers will be measured by changes from baseline in activated and memory T cells, interferon, interferon inducible factors, and CD4 and CD8 T cell infiltration. Time points for collection are specified in Table 5.5A and Table 5.5B.

8.3.2 Secondary Endpoint(s)

8.3.2.1 Safety

The secondary objective relates to safety and tolerability of nivolumab and nivolumab in combination of ipilimumab in subjects with advanced melanoma. These will be measured by the following endpoints:

Incidence rate of adverse events, serious adverse events, and deaths: all non-serious adverse events will be collected from Day 1 until 100 days after the subjects last dose of therapy or until they discontinue the study as per Section 3.1. All serious adverse events must be collected from the date of the subjects' written consent until 100 days after discontinuation of dosing or until they discontinue the study as per Section 3.1.

Occurrence of clinical laboratory test abnormalities including hematology and serum chemistry abnormalities assessed at specified timepoints as designated in the Time and Events Section (Section 5.1). Safety labs are listed in Section 5.3.1.

Vital signs: Changes in vital signs relative to baseline including blood pressure and heart rate measurements. These will be measured at time points designated in the Time and Events Section (Section 5.1).

8.3.2.2 Efficacy

The secondary objective relating to efficacy is to describe the anti-tumor activity of nivolumab and nivolumab in combination with ipilimumab in subjects with advanced melanoma. This objective will be measured by the following endpoints based on RECIST 1.1 criteria (Appendix 2). Disease evaluation will be performed at baseline, and then approximately every 8 weeks until disease progression or treatment discontinuation, whichever happens later.

The best overall response (BOR), computed for all treated subjects, is defined as the best response designation over the study as a whole, recorded between the dates of first dose until the last tumor assessment prior to subsequent therapy. CR or PR determinations included in the BOR assessment must be confirmed by a second scan performed no less than 4 weeks after the criteria

for response are first met. For those subjects who have surgical resection, only pre-surgical tumor assessments will be considered in the determination of BOR.

The objective response rate (ORR) is defined as the proportion of subjects with a BOR of CR or PR divided by the number of treated subjects (or response-evaluable subjects).

The Progression Free Survival Rate (PFSR) is defined as the probability of a subject remaining progression free or survival to time t, where t=24 weeks. This probability will be calculated by the product limit method (Kaplan-Meier estimates) which takes into account censored data.

The duration of response, computed for all treated subjects with a BOR of CR or PR, is defined as the time between the date of first response and the date of disease progression or death, whichever occurs first. For those subjects who remain alive and have not progressed or received subsequent therapy, duration of response will be censored on the date of last tumor assessment. For subjects who receive subsequent therapy prior to documented progression, duration of response will be censored on the date of subsequent therapy.

Progression free survival (PFS), computed for all treated subjects, is defined as the time between date of first dose of study therapy and date of progression or death, whichever occurs first.

8.4 Analyses

Subjects who were randomized to Arm C (ipilimumab monotherapy) prior to Amendment 06 may not be included in the analysis, but will be listed separately.

8.4.1 Demographics and Baseline Characteristics

Frequency distributions of gender, race, age category, race, ethnicity, and ECOG status, will be tabulated by cohort/arm. Summary statistics for age, body weight, height, body mass index (BMI) will be provided by cohort/arm.

8.4.2 Efficacy Analyses

All available tumor measurement data will be listed. Individual best overall response (BOR) will be listed and tabulated by cohort. The objective response rate (ORR), and corresponding 90% confidence intervals will be reported by cohort/arm.

Medians and corresponding two-sided 95% confidence intervals will be reported for duration of response, PFS, and OS by cohort and analyzed using Kaplan-Meier methods. Estimated PFSR at

24 weeks (by Kaplan-Meier methods) and 90% confidence intervals (based on Greenwood's formula) will be reported.

Cohort 1 and Arm B (nivolumab monotherapy with CTLA4 naive patient) will be combined for efficacy analyses.

Efficacy analyses will be performed separately for the populations of all treated subjects and response-evaluable subjects.

8.4.3 Safety Analyses

All recorded adverse events will be listed and tabulated by system organ class, preferred term, and cohort/arm and coded according to the most current version of MedDRA. The incidence of adverse events will be reviewed for potential significance and clinical importance. Vital signs and clinical laboratory test results will be listed and summarized by cohort/arm. Any significant physical examination findings and results of clinical laboratory tests will be listed. The incidence of infusion reactions will be reviewed to assess the safety and tolerability of reduced infusion times for nivolumab and nivolumab in combination with ipilimumab.

ECG readings will be evaluated by the investigator and abnormalities, if present, will be listed.

8.4.4 Pharmacokinetic Analyses

The following pharmacokinetic parameters of nivolumab and ipilimumab derived from serum concentration time profiles of subjects will be included for PK analyses:

Cmax - Maximum observed serum concentration

Tmax - Time of maximum observed serum concentration

AUC(0-T) -Area under the plasma concentration-time curve from time zero to the last time of the last quantifiable concentration

Cmin - Serum concentration achieved at the end of dosing interval (trough concentration)

Ceoinf - Serum concentration achieved at the end of the infusion

Summary statistics for serum nivolumab and ipilimumab concentrations (including Cmin and Ceoinf) will be tabulated by cohort/arm, study day, and time. Summary statistics will be provided for pharmacokinetic parameters for nivolumab and ipilimumab (Cmax, AUC(0-T) and Tmax) by cohort/arm. Geometric means and coefficients of variation will be presented for Cmax, and AUC (0-T). Medians, minima, and maxima values will be presented for Tmax. Part 1 Cohort 1 and Part 3 Arm B (nivolumab monotherapy with CTLA4 naive subjects) may be combined for PK analyses if appropriate. Part 2 Arm A and Part 3 Arm A (combination therapy with CTLA4 naive subjects) may also be combined for PK analyses if appropriate.

In addition, pharmacokinetic data from this study may be combined with data from other studies for a population PK model, which may be presented in a separate report.

[redacted]

8.4.8 Outcomes Research Analyses

Not applicable to this study.

[redacted]

8.5 Interim Analyses

Administrative interim analyses may be performed at several times prior to completion of the study in order to facilitate program decisions and to support presentations or publications.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

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

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

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

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

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

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

9.1.2 Monitoring

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

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

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

9.1.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

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

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

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

9.2.2 Study Drug Records

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

- amount received and placed in storage area
- amount currently in storage area
- label ID 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
- non-study disposition (e.g., lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to the Sponsor
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product (IP) dispensing/accountability, as per the Delegation of Authority Form.

The Sponsor 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 reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

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

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

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

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by a qualified physician who is an investigator or sub investigator. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by the Sponsor. 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 considering the following criteria:

- Subject recruitment (e.g., among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (e.g., among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to the Sponsor. Any publications or abstracts arising from this study require approval by the Sponsor prior to publication or presentation and must adhere to the Sponsor's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to the Sponsor at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. Sponsor shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

10 GLOSSARY OF TERMS

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

11 LIST OF ABBREVIATIONS

Abbreviation	Term
ALT	alanine aminotransferase
AIDS	acquired immunodeficiency syndrome
APC	Antigen-presenting cells
AST	Aspartate aminotransferase
BOR	Best overall response
BORR	Best overall response rate
BP	Blood pressure
CI	Confidence interval
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4
DC	Dendritic cells
DCF	Data clarification form
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DTIC	Dacarbazine
ECG	Electrocardiogram
EDC	Electronic data capture
FDA	Food and Drug Administration
FFPE	Formalin fixed paraffin embedded
FSH	Follicle stimulating hormone
GCP	Good clinical practices
GMP	Good manufacturing practices
GCSF	Granulocyte colony stimulating factor
GI	Gastrointestinal
GM-CSF	Granulocyte macrophage colony stimulating factor
HBV SAg	Hepatitis B virus surface antigen

Abbreviation	Term
HCV RNA	hepatitis C virus ribonucleic acid
HIPAA	Health Information Portability and Accountability Act
HIV	human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN	Interferon
IL-2	Interleukin-2
IULN	Institutional upper limit of normal
IP	Investigational product
IRB	Institutional Review Board
IV	Intravenous
LFTs	Liver function tests
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MEL	Metastatic melanoma
MLR	Mixed lymphocyte reaction
MRI	Magnetic resonance imaging
ORR	Objective response rate
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PR	Partial response
PVG	Pharmacovigilance
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RT	Radiation therapy
SAE	Serious adverse event

Abbreviation	Term
SD	Stable disease
SLD	Sum of longest diameters
SNP	Single nucleotide polymorphism
SOP	Standard operating procedures
SUV	Standardized uptake value
TCR	T-cell receptor(s)
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
WBC	White blood cell
WOCBP	Women of child bearing potential

APPENDIX 2 RECIST 1.1

1 ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the *overall tumor burden at baseline* and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable tumor lesion. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

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

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

1.2 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 in not measurable by reproducible imaging techniques.

1.3 Special considerations regarding lesion measurability

1.3.1 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.

1.3.2 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 non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

1.3.3 Lesions with prior local treatment

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

1.4 Specifications by methods of measurements

1.4.1 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 30 days before the beginning of the treatment.

1.4.2 Method of assessment

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

1.4.2.1 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.

1.4.2.2 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.

1.4.2.3 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 by both 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.

1.4.2.4 Ultrasound

Ultrasound is ***not*** useful in 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.

1.4.2.5 Endoscopy, laparoscopy

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

2 BASELINE DOCUMENTATION OF 'TARGET' AND 'NON-TARGET' LESIONS

2.1 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.

2.1.1 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.

2.2 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 record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

3 TUMOR RESPONSE EVALUATION

3.1 Evaluation of target lesions

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

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

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

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

3.1.1 Special notes on the assessment of target lesions

3.1.1.1 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.

3.1.1.2 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 (e.g. 2 mm). If the radiologist is able to provide an actual measurement, that should be recorded, even if it is below 5 mm.

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

- if it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- if the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (note: in case of a lymph node believed to be present and faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).

3.1.1.3 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 may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly

coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

3.2 Evaluation of non-target lesions

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

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

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

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

3.2.1 Special notes on assessment of non-target lesions

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

3.2.1.1 When the subject also has measurable 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 quality for unequivocal progression status.

3.2.1.2 When the subject has only non-measurable disease

- To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening such that 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.
- Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are non-measurable) a useful test that can be applied when assessing subjects for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'.
- If 'unequivocal progression' is seen, the subject should be considered to have had overall PD at that point.

3.2.1.3 Tumor markers

Tumor markers *alone* cannot be used to assess objective tumor responses. If markers are initially above the upper normal limit, however, they must normalize in order for a subject to be considered as having attained a complete response.

3.3 New lesions

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

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

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

3.3.1 FDG-PET evaluation

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

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

4 RESPONSE CRITERIA

4.1 Time point response

A response assessment should occur at each time point specified in the protocol.

For subjects who have **measurable disease** at baseline Table 4.1 provides a summary of the overall response status calculation at each time point.

Table 4.1. 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.

4.1.1 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.

4.1.2 Confirmation Scans

- **Verification of Response:** *Confirmation of PR and CR is required within 4 weeks to ensure responses identified are not the result of measurement error.*

4.2 Best overall response: All timepoints

The *best overall response* is determined once all the data for the subject is known. It is the best response recorded from the start of the study treatment until the end of treatment taking into

account any requirement for confirmation. 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.

Best response is defined as the best response across all time points with subsequent confirmation. Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later).

In this circumstance, the best overall response can be interpreted as specified in Table 4.2. When SD is believed to be best response, it must meet the protocol specified minimum time from baseline. Measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

Table 4.2. Best overall response when confirmation of CR and PR *IS* required.

Overall response	Overall response	BEST overall response
First time point	**Subsequent time point**	
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable.

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

4.3 Duration of response

4.3.1 Duration of overall response

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

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

4.3.2 Duration of stable disease

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

APPENDIX 3 GUIDANCE ON CONTRACEPTION

ACCEPTABLE METHODS FOR PROTOCOLS WITH A TERATOGENIC DRUG OR WHEN THERE IS INSUFFICIENT INFORMATION TO DETERMINE TERATOGENICITY

(CHOOSE ONE OF THE FOLLOWING 4 OPTIONS)[a]

OPTION 1: Any TWO of the following methods

- Hormonal methods of contraception[b, c, d]
- IUD[c, d, e]
- Vasectomy[d, f]
- Tubal Ligation[d]
- A Barrier method (Female or Male Condom with spermicide, Cervical Cap with spermicide, Diaphragm with spermicide)

OPTION 2: Male condom (with spermicide) and diaphragm[g]

OPTION 3: Male condom (with spermicide) and cervical cap[g]

OPTION 4: Complete Abstinence [h]

[a] The theoretical failure rate for any of the options listed is considerably less than 1% per year

[b] Excludes progestin-only pills

[c] Hormonal contraceptives may not be used for contraception unless a drug-drug interaction study has demonstrated that the pharmacokinetics of the hormone based contraceptive has not been adversely affected by the investigational drug in the protocol or there is compelling evidence to substantiate that investigational product(s) or con-meds will not adversely affect contraception effectiveness. The PK scientist and MST chair must agree that the use of hormone-based contraception is safe and efficacious for WOCBP. The use of hormone-based contraceptives is not otherwise restricted

[d] A highly effective method of birth control with a failure rate less than 1% per year

[e] IUDS used should have a failure rate less than 1% (highly effective method), such as Mirena and ParaGard

[f] Must be at least 90 days from date of surgery with a semen analysis documenting azoospermia

[g] These 2 barrier methods together are acceptable for a teratogenic drug

[h] Complete abstinence is defined as the complete avoidance of heterosexual intercourse. Complete abstinence is an acceptable form of contraception for all study drugs and must be used throughout the duration of study and for the duration of time as specified in the protocol. It is not necessary to use a second method of contraception when complete abstinence is elected. Subjects who choose complete abstinence must continue to have pregnancy tests, as specified in the protocol. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

UNACCEPTABLE METHODS OF CONTRACEPTION
No method
Withdrawal
Rhythm
Vaginal Sponge
Any barrier method without spermicide
Spermicide
Progestin only pills
Concomitant use of female and male condom

In countries where spermicide is not available or its use is not considered compatible with male condoms, use of a male condom without spermicide in conjunction with a hormonal method, IUD, or tubal ligation will be acceptable to fulfill this recommendation. Any barrier method when used alone (without spermicide) or the concomitant use of a female and male condom, is not considered a sufficient method of contraception, as each carries a failure rate of >1%.

Women of childbearing potential (WOCBP) receiving BMS-936558 (nivolumab) will be instructed to adhere to contraception for a period of 23 weeks after the last dose of investigational product. Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 31 weeks after the last dose of investigational product. These durations have been calculated using the upper limit of the half-life for BMS-936558 (nivolumab) (25 days) and are based on the protocol requirement that WOCBP use contraception for 5 half-lives plus 30 days and men who are sexually active with WOCBP use contraception for 5 half-lives plus 90 days after the last dose of BMS-936558 (nivolumab).

APPENDIX 4 NIVOLUMAB MANAGEMENT ALGORITHMS

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

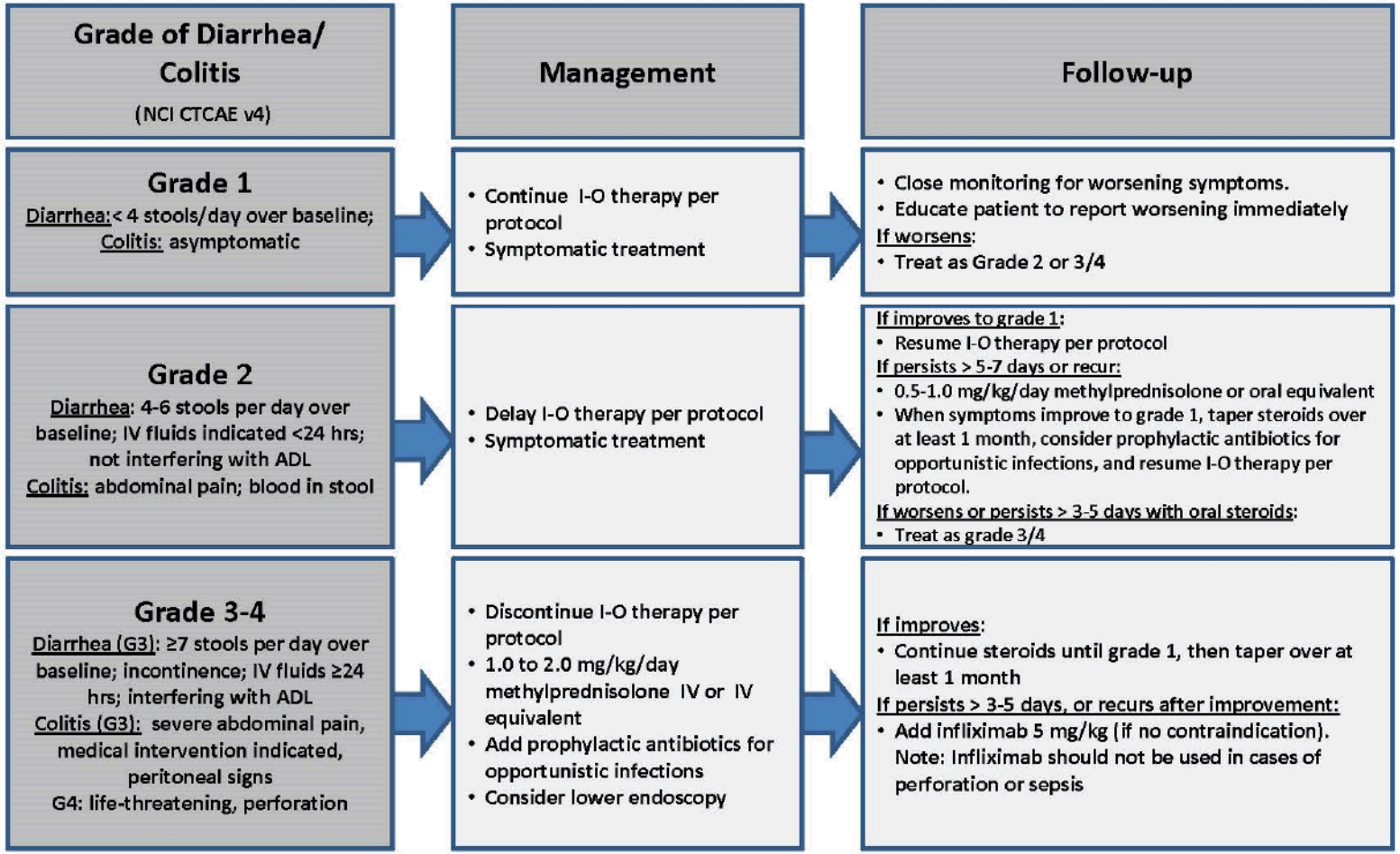
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

GI Adverse Event Management Algorithm

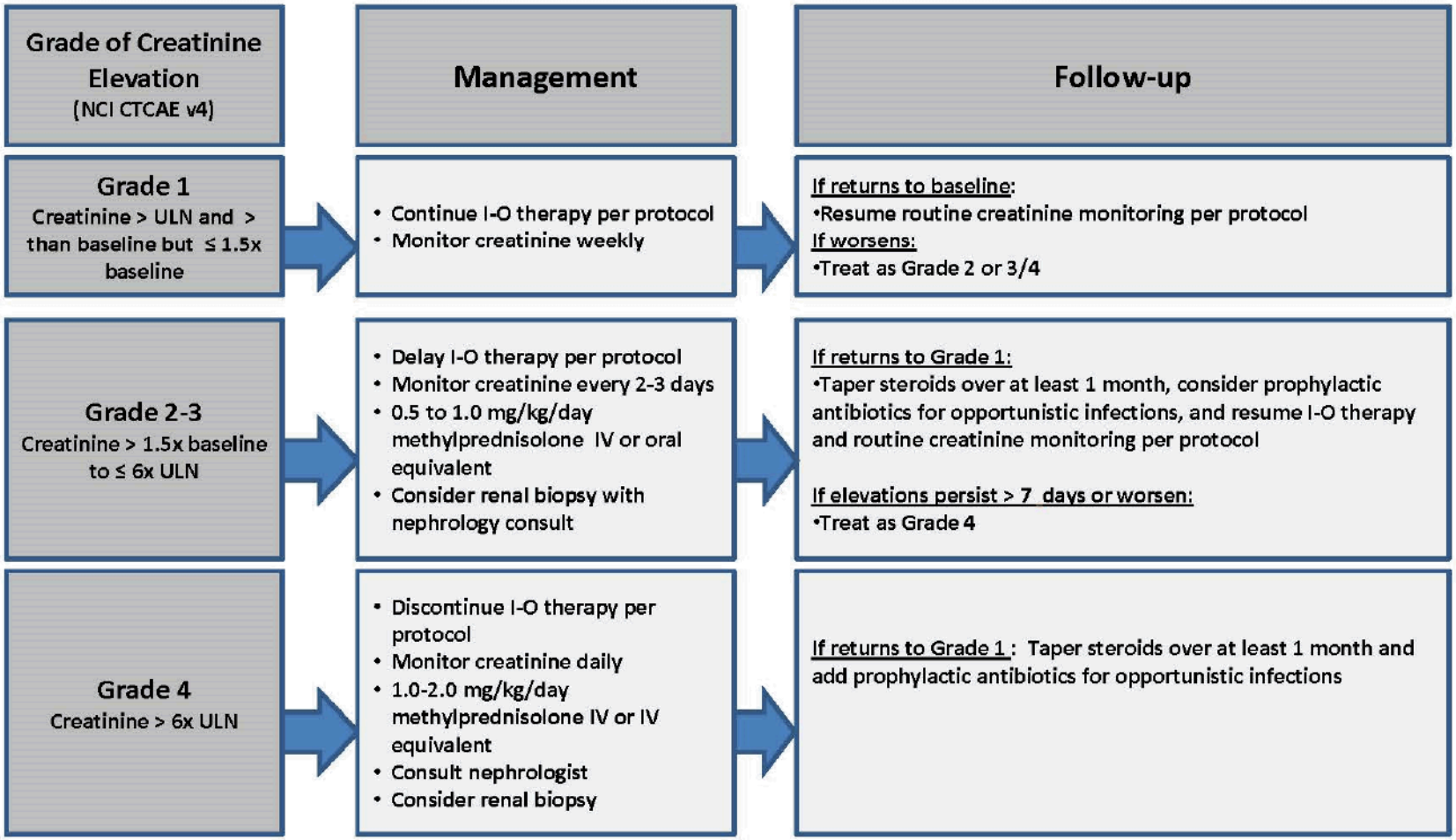
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



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

Renal Adverse Event Management Algorithm

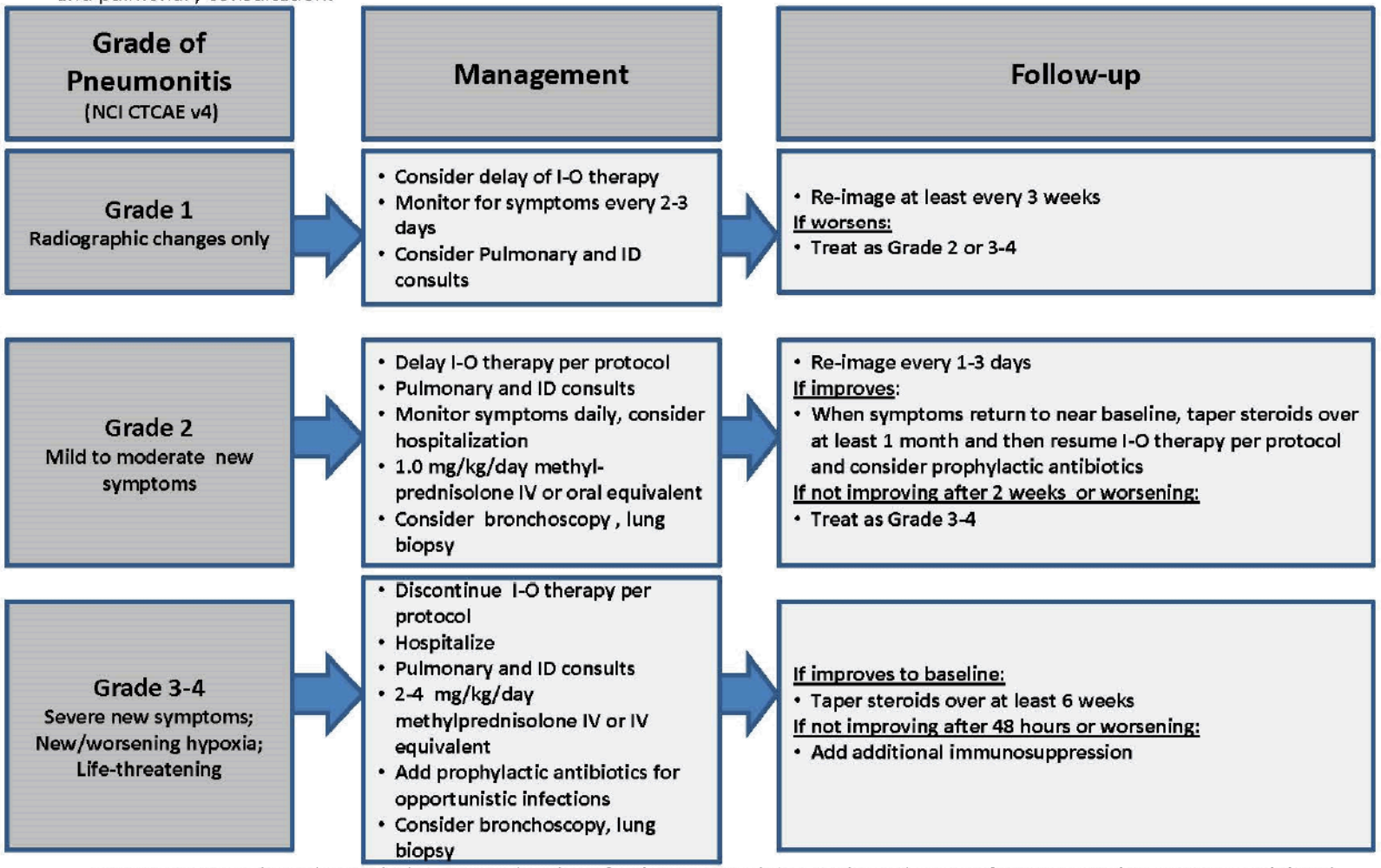
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



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

Pulmonary Adverse Event Management Algorithm

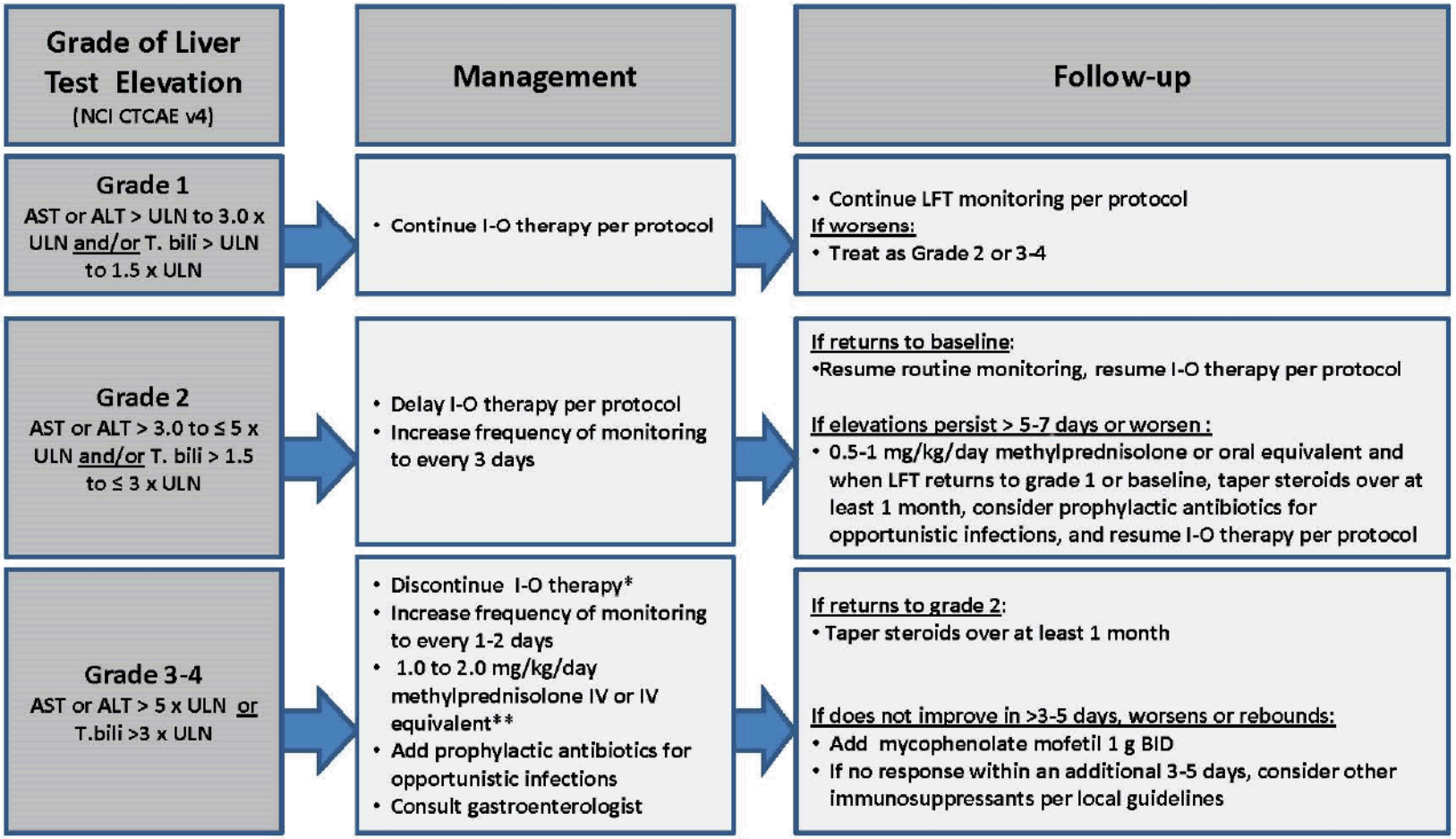
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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

Hepatic Adverse Event Management Algorithm

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



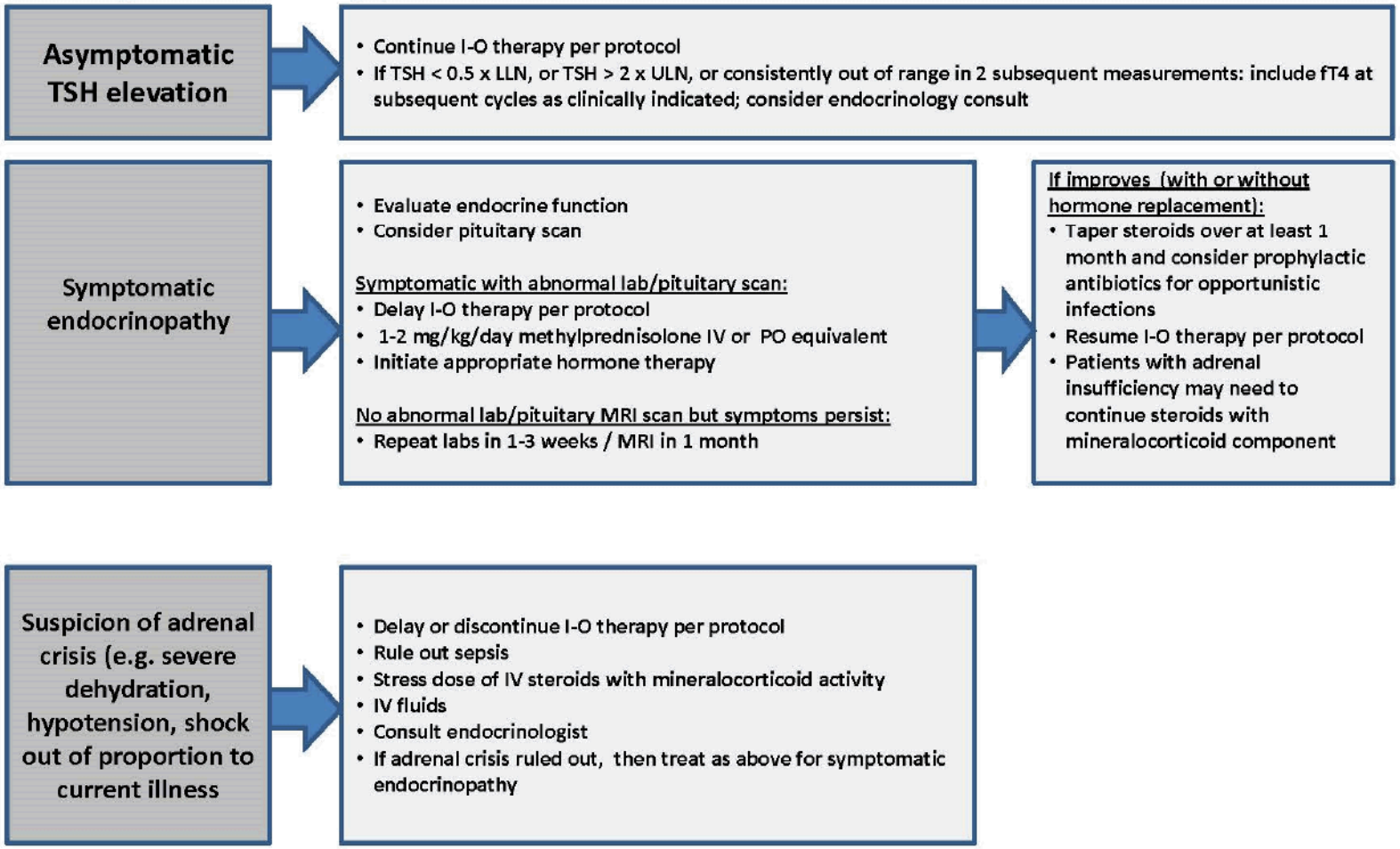
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

*I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.

**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Endocrinopathy Management Algorithm

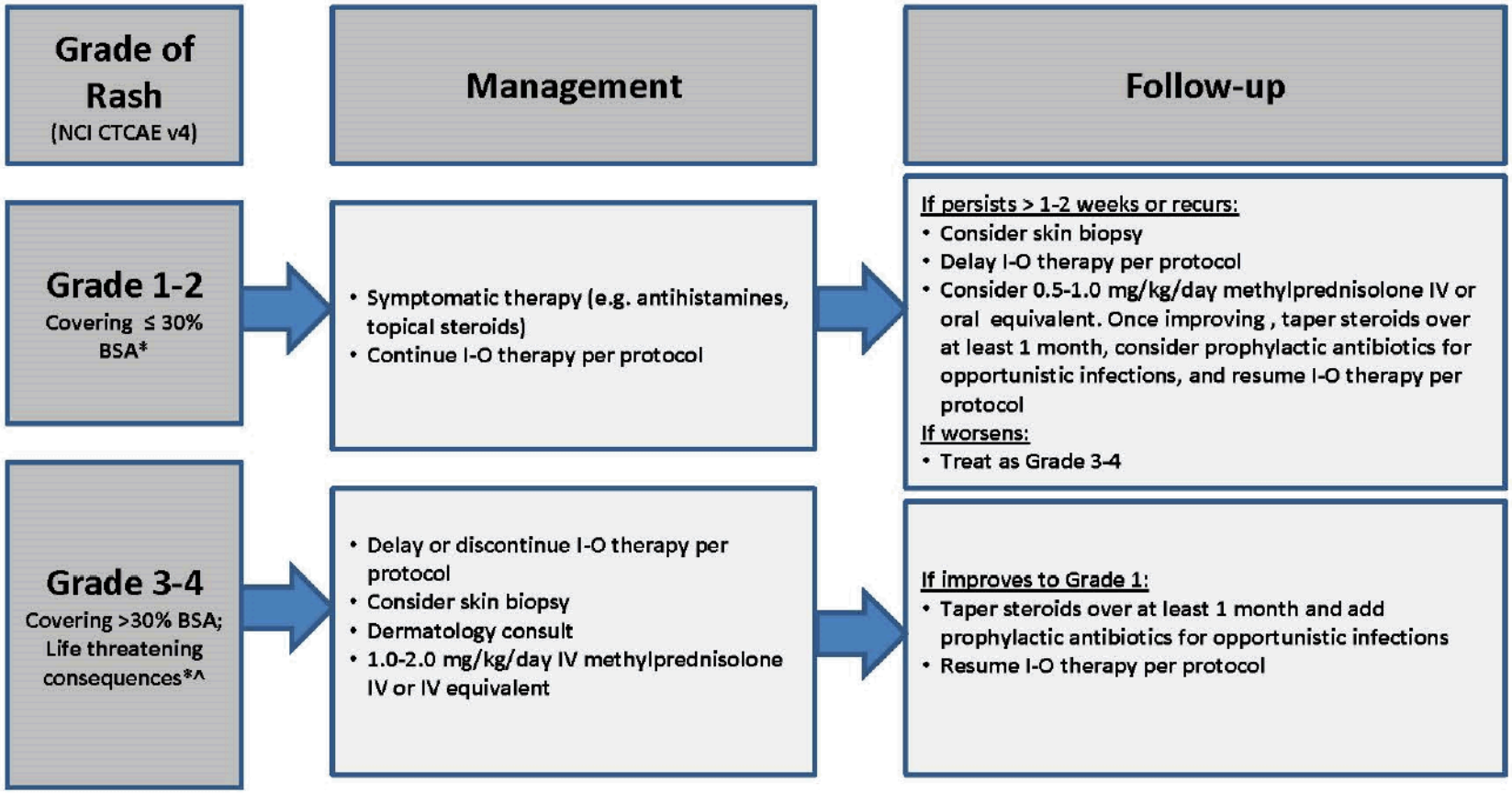
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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

Skin Adverse Event Management Algorithm

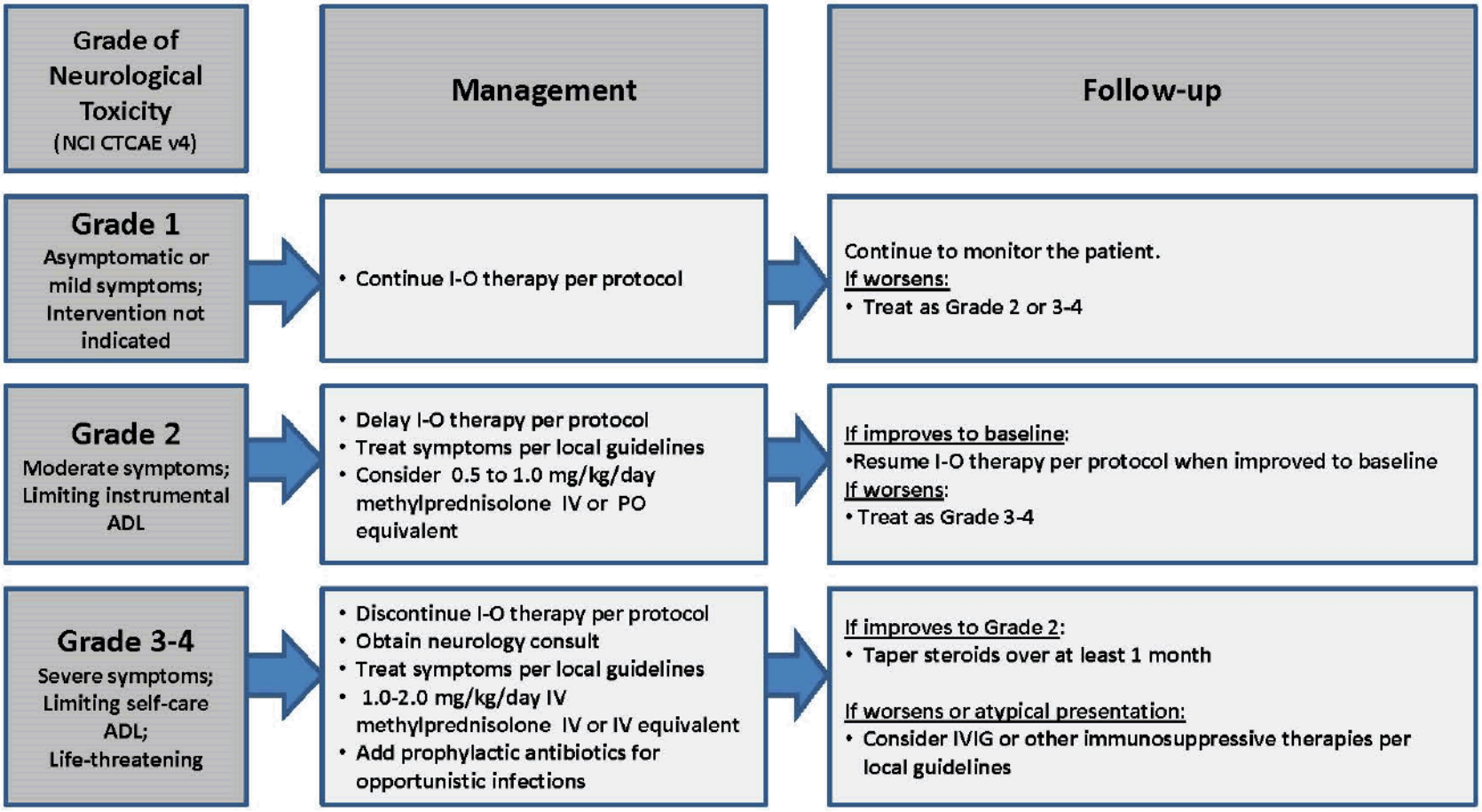
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.
^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

Neurological Adverse Event Management Algorithm

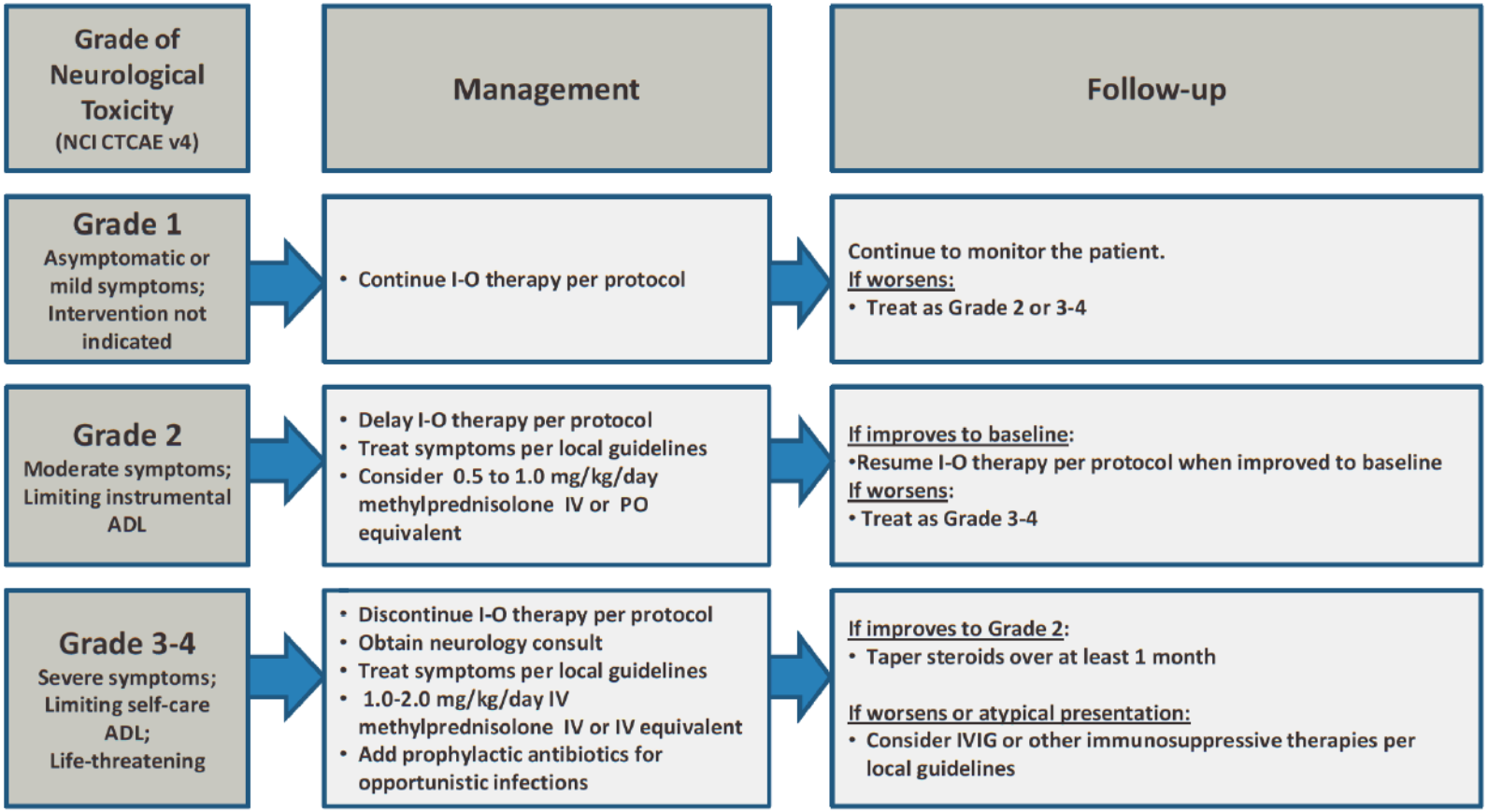
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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

Neurological Adverse Event Management Algorithm

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



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