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Revised Date 13-Nov-2017

Clinical Protocol CA209204

A Multi-Center Phase 2 Open-Label Study to Evaluate Safety and Efficacy in Subjects with Melanoma Metastatic to the Brain treated with Nivolumab in Combination with Ipilimumab followed by Nivolumab Monotherapy

CheckMate 204: **CHECK**point pathway and nivolu**MA**b clinical **T**rial **E**valuation 204

Revised Protocol Number: 03
Incorporates Administrative Letters 03 and 04

Study Director/Medical Monitor

Sheena Demelo, MD

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

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 03	13-Nov-2017	Major Changes • Addition of progression free survival (PFS) as a secondary objective to align with nivolumab program-wide objectives. • Expansion of secondary [redacted] objectives to align with data reported for this study. • All radiologic images will be transmitted to a centralized imaging core laboratory. Details of the review conducted by an Independent Radiologic Review Committee (IRRC) are outlined in a separate CA209204 Imaging Review Charter. • Intracranial and extracranial replace brain and systemic, respectively, for protocol-specific references throughout the document.
Administrative Letter 04	10-Jan-2017	Clarification of dosing in study design figure: nivolumab and ipilimumab should be dosed every 3 weeks (Q3) during the Induction Phase of protocol treatment.
Administrative Letter 03	28-Oct-2016	Administrative change: study personnel.
Revised Protocol 02	15-Aug-2016	Incorporates Global Amendment 02
Global Amendment 02	15-Aug-2016	Major Amendment 02 Changes • Eligibility criteria modified to allow a second cohort of symptomatic subjects with melanoma metastatic to the brain as defined in the revised Inclusion/Exclusion Criteria. • Efficacy objectives will be based on Investigator review at the study sites rather than on review at a central facility. All radiologic images will be sent to a centralized imaging core laboratory for storage and potential future central reading. [redacted] • The second interim analysis has been removed from the study design. • Treatment for all enrolled patients who continue to show response is permitted for up to a maximum of 24 months. • Follow-up period has been extended to 5 years from the date of first treatment. [redacted] • Subjects must be re-consented to receive treatment beyond progression • Guideline added for subjects to discontinue treatment beyond progression. • Inclusion criteria updated to include criteria for symptomatic patients. • Minor changes within inclusion criteria for reproduction to comply with study-drug program-wide standard. • Alignment of on-study laboratory assessments. • Statistical section now includes additional analyses by cohort:

Document	Date of Issue	Summary of Change
		Cohort A: asymptomatic subjects (approximate cap of 90) Cohort B: symptomatic subjects who may be on steroids (approximate cap of 20). [redacted]
Revised Protocol 01	28-Aug-2015	Incorporates Global Amendment and Administrative Letters 01 and 02.
Global Amendment 01	28-Aug-2015	Major Amendment 01 Changes: • Subjects with melanoma metastatic to the brain with and without systemic lesions are now eligible for the study • Prior treatment allowed: BRAF and/or MEK inhibitors for advanced disease • Prior treatment allowed: patients who received ipilimumab as adjuvant therapy must have a 6 month washout before receiving dosing on this study [redacted] • Enrolled subjects may receive stereotactic radiation therapy (SRT) (single episode) for progression of up to 3 brain lesions • Brain edema or post SRT steroid treatment specified as ≤ 16 mg dexamethasone PO daily tapered in ≤ 4 weeks • Two interim analyses incorporated into the study design • Steering Committee replaces safety committee • Modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1) incorporated in response algorithm for brain tumors • Immune-related Response Criteria and the Protocol-defined response criteria have been removed from the study • Subsections in Section 5.4 Efficacy Assessments that also appear in Appendix 3 are now deleted from protocol body [redacted] • Appendix 3 modified to reflect changes made for brain lesions.
Administrative Letter 02	15-Jul-2015	Modified the requirements for pre-treatment tumor tissue within the eligibility criteria. This change allows for submission of archival tumor tissue when an extracranial metastasis tissue specimen collected after the most recent prior systemic therapy is not available or cannot be obtained by biopsy.
Administrative Letter 01	13-Mar-2015	Corrects IND Number for Protocol CA209-204
Original Protocol	22-Sep-2014	Not applicable

[redacted]

[redacted]

[redacted]

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	[redacted]
Title Page	Update of study personnel	
Throughout the protocol	• Intracranial and extracranial replace brain and systemic, respectively, for protocol-specific references throughout the document.	
• Synopsis, Objectives, Primary, Secondary, [redacted] • Synopsis, Study Assessments • Synopsis, Statistical Considerations, Efficacy Analyses • Section 1.3.2 Secondary Objectives [redacted] • Section 8.3.1.1 Best Overall Response (BOR) per Subject. Endpoint Definitions	• Addition of progression-free survival (PFS) as a secondary objective • Secondary [redacted] objectives have been expanded. Definitions for new objectives have been included. • Sensitivity analyses using IRRC-assessed Clinical Benefit Rate (CBR) and Overall Response Rate (ORR) will also be performed.	

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 03

Section Number & Title	Description of Change	[redacted]
• Section 8.4.2 Secondary Endpoints [redacted] • Section 8.5.2 Primary Efficacy Analyses • Section 8.5.3 Secondary Efficacy Analyses [redacted]		
• Synopsis, Study Design and Figure; • Section 3.1 Study Design and Duration; Figure 3.1-1 CA209204 Study Design	• Subjects will be followed for 3 years after first treatment rather than for 5 years	
• Synopsis, Study Assessments • Section 3.1 Study Design and Duration • Section 5.8 Results of Central Assessments	• Central review of all images will be conducted by an Independent Radiologic Review Committee (IRRC) specified in the Imaging Review Charter.	
• Section 3.1 Study Design	• The following three sections were added: Section 3.1.1, Screening Phase; Section 3.1.2, Treatment Phase; Section 3.1.3 Follow-up Phase.	
• Section 4.5.2, Dose Delay Criteria	• Sentence added to specify that tumor assessments are to be conducted per protocol even if a dose is delayed	
• Section 4.5.7 Treatment Beyond Initial Radiological Assessment of Disease Progression	• Revision of description of treatment beyond progression. • Progression of disease should be verified in cases where progression is	

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	[redacted]
• Section 5.4.3 Confirmation of Scans	equivocal.	
• Section 5.1, Flow Chart/ Time and Events Schedule, Table 5.1-2 On-study Assessments Cycles 1 and 2 (CA209204) • Section 5.1, Flow Chart/ Time and Events Schedule, Table 5.1-3 On-study Assessments Cycles 1 and 2 (CA209204)	• A note in the table header now specifies that tumor assessments are to be conducted per protocol even if a dose is delayed. The footnote regarding dose delay and study assessments has been removed.	
• Section 5.1, Flow Chart/ Time and Events Schedule, Table 5.1-1 Screening Assessments (CA209204) • Section 5.1, Flow Chart/ Time and Events Schedule, Table 5.1-1 On-study Assessments Cycles 1 and 2 (CA209204) • Section 5.1, Flow Chart/ Time and Events Schedule, Table 5.1-3 On-study Assessments Cycle 3 and Beyond (CA209204) • Section 5.1, Flow Chart/ Time and Events Schedule, Table 5.1-4 Follow-up Assessments (CA209204)	• Presentation of Tumor Assessment aligned to program-wide standards. No content change.	
• Section 5.4 Efficacy Assessments	• Revised to align with Schedule of Activities. No content change.	

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 03		[redacted]
Section Number & Title	**Description of Change**	
• Section 8.5.9, Interim Analyses	• Revised based on results of interim analyses.	
Appendix 3: Image Assessment Criteria 1.1: Measurability of tumor	Required thickness of MRI scan slice for intracranial lesions ≤10 mm LD and >10 mm LD are now specified in second bullet.	
Throughout the document.	Minor editorial or formatting changes/corrections	

SYNOPSIS

Clinical Protocol CA209204

Protocol Title: A Multi-Center Phase 2 Open-Label Study to Evaluate Safety and Efficacy in Subjects with Melanoma Metastatic to the Brain treated with Nivolumab in Combination with Ipilimumab followed by Nivolumab Monotherapy CheckMate 204: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 204

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

Nivolumab administered IV over 60 minutes at 1 mg/kg and ipilimumab administered IV over 90 minutes at 3 mg/kg every 3 weeks for 4 doses (combination regimen) followed by nivolumab administered IV over 60 minutes at 3 mg/kg every 2 weeks until progression or discontinuation due to toxicity

Study Phase: Phase 2

Research Hypothesis: Treatment with nivolumab combined with ipilimumab followed by nivolumab monotherapy will provide clinical benefit to subjects with melanoma metastatic to the brain.

Objectives:

Study objectives will be applied for all treated subjects (Cohort A and Cohort B).

Primary, secondary, [redacted] endpoints and safety analyses will be reported in the treated subjects, for overall population, by cohorts (asymptomatic and symptomatic), and by subgroup (prior to study with or without SRT and on study with or without SRT).

Primary Objective: To assess intracranial clinical benefit rate (CBR, defined as complete response [CR] + partial response [PR] + stable disease [SD]) $\geq$ 6 months in subjects with melanoma metastatic to the brain per modified RECIST 1.1 criteria.

Secondary Objectives:

- To assess the extracranial clinical benefit rate defined as CR+PR+SD $\geq$ 6 months (per RECIST 1.1 criteria)
- To assess intracranial objective response rate (ORR), intracranial progression-free survival (PFS) per modified RECIST 1.1 criteria
- To assess extracranial ORR, extracranial PFS per RECIST 1.1 criteria
- To assess global CBR, global ORR, global PFS per a combination of modified RECIST 1.1 criteria for intracranial lesions and RECIST 1.1 for extracranial disease
- To assess overall survival (OS)
- To evaluate the intracranial-specific safety and tolerability of the combination regimen in patients with or without stereotactic radiotherapy (SRT) received prior to study entry, or on study.

[redacted]

[redacted]

Study Design: This is an open-label, multi-site, Phase 2 study of nivolumab combined with ipilimumab followed by nivolumab monotherapy for the treatment of subjects with melanoma metastatic to the brain.

Cohort A comprises subjects with histologically-confirmed malignant melanoma with asymptomatic intracranial metastases with or without measurable extracranial disease. Per Amendment 02, August 2016, the patient population was expanded to include Cohort B, which will enroll approximately 20 patients with symptomatic intracranial metastases who may be on steroids per protocol specifications. Symptomatic patients who are not on steroids are also eligible for Cohort B.

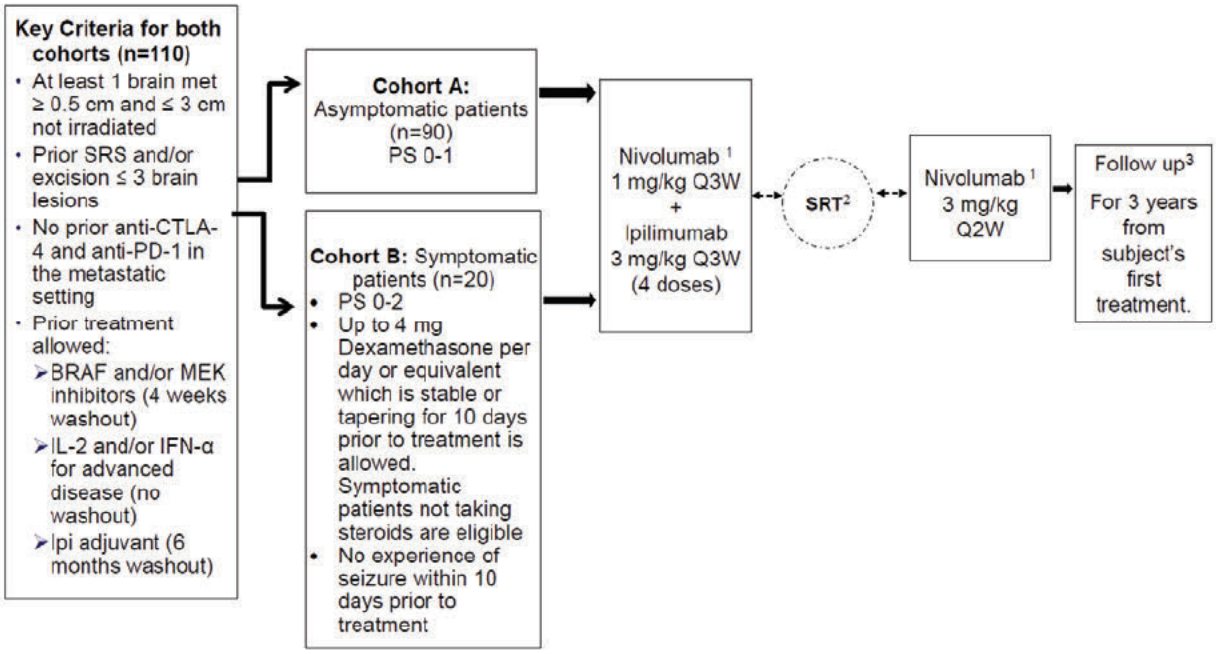
Asymptomatic subject who are enrolling into Cohort A and become symptomatic during the screening evaluations may be considered for enrollment into Cohort B if they meet all other criteria for Cohort B. No crossover between cohorts is permitted after the start of treatment.

All patients will be treated with the combination regimen of nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg Q3W (4 doses), followed by nivolumab monotherapy (3 mg/kg Q2W) for a maximum of 24 months, or until progression or unacceptable toxicity. The study will close after the last enrolled subject completes 3 years of follow up from the date of first treatment or the study is discontinued by the sponsor.

At any time, if the safety profile of an enrolled subject suggests an unfavorable risk/benefit profile, a decision will be made by the sponsor in conjunction with the investigators whether to pause or continue enrollment. The steering committee will be informed if a safety signal emerges and will be informed of the results of the planned interim analysis.

The use of SRT (single episode) for disease progression of ≤ 3 intracranial lesions is permitted in this study per protocol-defined guidelines. Any subject who receives SRT while on study will be observed for a protocol-defined period before treatment with the study drug(s) can be resumed. The length of the observation period is determined by when in the course of treatment the subject receives SRT - during induction (nivolumab plus ipilimumab) or during maintenance treatment (nivolumab monotherapy). NOTE: To continue on-study after SRT, at least 1 non-irradiated target lesion must remain after SRT treatment.

Any subject who meets criteria for discontinuation following SRT will proceed to follow-up. All subjects who have completed 24 months of treatment with study drugs, or have been discontinued from treatment will continue to be followed for safety, progression, and overall survival for up to 3 years from the date of the subject's first treatment.



SRT = stereotactic radiotherapy

[1] Subjects may continue to receive on study treatment for a maximum of 24 months or until confirmed progression or unacceptable toxicity or patient withdrawal of consent. After discontinuation from treatment with study drug(s) subjects will proceed to follow-up. Subjects who continue to respond at the end of on study treatment may be prescribed study medication through commercial supply or under appropriate care per investigator.

[2] Use of SRT for progression of ≤ 3 intracranial lesions will be allowed per protocol-specific guidelines. Subjects who require SRT for a second episode of disease progression will be discontinued from treatment and proceed to follow-up.

[3] All subjects who are discontinued from treatment with study drug(s) or have received the maximum of 24 months of treatment will proceed to follow-up.

Study Population:

Cohort A (asymptomatic) Patients with histologically confirmed metastatic melanoma presenting with intracranial metastases and at least 1 measurable index intracranial metastasis ≥ 0.5 cm and ≤ 3 cm in diameter that has not been previously irradiated. No clinical requirement for local intervention (surgery, radiosurgery, corticosteroid therapy) or other systemic therapy.

Approximate enrollment in Cohort A is 90 patients.

Cohort B (symptomatic): Patients with histologically confirmed metastatic melanoma presenting with symptomatic intracranial metastases who may be on steroids with doses no higher than a total daily dose of 4 mg of dexamethasone or equivalent that is stable or tapering within 10 days prior to treatment. Patients who are symptomatic and are not being treated with steroids are also eligible. Patients enrolled in Cohort B must have at least 1 measurable index intracranial metastasis ≥ 0.5 cm and ≤ 3 cm in diameter that has not been previously irradiated, must not require immediate local therapy (SRT or surgery within 3 weeks prior to first treatment), performance status must be 0-2, and no experience of seizure within 10 days prior to first treatment.

Subjects with a history of whole brain irradiation are not eligible for this study.

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

Study Drugs for CA209204		
Medication	**Potency**	**IP/Non-IP**
Nivolumab Solution for Injection	100 mg (10 mg/mL)	IP
Ipilimumab Solution for Injection	200 mg (5 mg/mL)	IP

Study Assessments: Response to treatment will be assessed in the intracranial and extracranial compartments and will be evaluated by serial radiographic assessment every 6 weeks for the first year and every 12 weeks thereafter until documented progression, withdrawal of consent, or the end of the study.

All efficacy objectives, including the primary efficacy objective, intracranial clinical benefit rate (CBR), defined as CR + PR + SD $\geq$ 6 months per the modified RECIST 1.1 criteria, will be based on Investigator assessment. Extracranial response will be based on RECIST 1.1. Global (intracranial plus extracranial) tumor burden response assessment will be assessed per a combination of modified RECIST 1.1 for intracranial lesions and RECIST 1.1 for extracranial disease per the modified RECIST 1.1 criteria, also Investigator evaluated. Secondary and exploratory objectives include responses in all compartments as specified above. In addition, 3-D MRI will be conducted and may be evaluated for exploratory study. All images will be evaluated at the site. As an exploratory objective, efficacy will also be assessed with the NANO scale for neurologic function.

All radiologic imaging from this study will be transmitted to a centralized imaging core laboratory for storage and analysis. Sites will be informed of quality issues or the need for repeat scanning via queries from the core lab. The details of the independent review performed by the Independent Radiologic Review Committee (IRRC) are outlined in a separate CA209204 Imaging Review Charter.

Safety will be evaluated for all treated subjects using the NCI CTCAE version 4.0. Safety assessments will be based on medical review of AE reports and the results of vital sign measurements, physical examinations, and clinical laboratory tests. Clinical decisions to continue or hold/discontinue therapy will be based on the judgment of the treating physician/principal investigator.

[redacted]

Statistical Considerations:

Sample Size: The sample size for the combination treatment of nivolumab plus ipilimumab is 110 subjects:

Cohort A: 90 patients (asymptomatic as defined under Study Population)
Cohort B: 20 patients (symptomatic as defined under Study Population)

All treated patients in Cohort A and Cohort B will contribute to the efficacy assessments. The planned sample size ensures that the maximum width of the exact 90% CI for any given CBR estimate does not exceed 18%.

A sample size of 110 achieves 80.4% power to detect an improvement of about 12% over the estimated CBR for non-investigational immunotherapies in similar patients, estimated to be about 40% or lower.

Endpoints: The primary efficacy endpoint is the intracranial clinical benefit rate (CBR, defined as CR + PR + SD $\geq$ 6 months) in subjects with malignant melanoma metastatic to the brain, treated with nivolumab combined with ipilimumab therapy.

Analyses: The analyses of primary, secondary, [redacted] endpoints and safety analyses will be reported in the treated subjects, for overall population, by cohorts (asymptomatic and symptomatic), and by subgroup (prior to study with or without SRT and on study with or without SRT).

Demographics and Baseline Characteristics: Demographic and baseline characteristics will be summarized using descriptive statistics for all treated subjects. Patients will be categorized into 4 subgroups according to their SRT status (prior to study with or without SRT and on study with or without SRT) and by cohorts (asymptomatic and symptomatic). The number of enrolled subjects will be summarized. Summarization will be provided for treated

subjects, for overall population, by cohorts (asymptomatic and symptomatic), and by subgroup (prior to study with or without SRT and on study with or without SRT).

Efficacy Analyses: All of the efficacy analyses will be summarized for the 4 subgroups (prior to study - with or without SRT and on study with or without SRT), for the overall group and by cohorts (asymptomatic and symptomatic).

The primary endpoint of intracranial CBR for the overall population, with its corresponding 90% exact confidence interval (CI) will be calculated by the Clopper-Pearson method. A sensitivity analysis using IRRC-assessed intracranial CBR will also be performed.

Secondary endpoints are as follows:

- Intracranial ORR and intracranial PFS per modified RECIST 1.1 criteria;
- Extracranial CBR, extracranial ORR, extracranial PFS per RECIST 1.1 criteria
- Global (intracranial +extracranial) CBR, global ORR, and global PFS per a combination of modified RECIST 1.1 criteria for intracranial lesions and RECIST 1.1 for extracranial disease
- Overall survival (OS).
- Safety and tolerability will be measured by the incidence of adverse events (AE), serious adverse events (SAE), deaths, and laboratory abnormalities.

Progression-free survival (PFS) is defined as the time between the date of first dose of study drug and the first date of documented progression, as determined by the investigator, or death due to any cause, whichever occurs first. Subjects who die without a reported progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on study tumor assessments and did not die will be censored on the date of first dose of study drug. Subjects who started anti-cancer therapy without a prior reported progression will be censored on the date of their last evaluable tumor assessment prior to the initiation of subsequent anti-cancer therapy.

Overall response rate (ORR) is defined as the number of subjects who achieve a best overall response (BOR) of complete response (CR) or partial response (PR) divided by the number of treated subjects.

The BOR is defined as the best response designation recorded between the date of first study dosing date and the date of progression, or the date of subsequent anticancer therapy (including tumor-directed radiotherapy and tumor-directed surgery), whichever occurs first. In this study, BOR is specified for the intracranial, extracranial, and global compartments based on the (1) modified RECIST 1.1 criteria (intracranial), (2) RECIST 1.1 criteria (extracranial), (3) combination of modified RECIST 1.1 criteria and RECIST 1.1 criteria (global). The BOR for each patient as determined by the IRRC is determined from a predefined set of rules specified within the Image Review Charter.

Median overall survival (OS) will be estimated using the Kaplan-Meier product-limit method. Overall survival curves will be plotted using the Kaplan-Meier method. The incidence of MRI-defined intracranial edema, hemorrhage, and increase in size before achievement of clinical benefit (pseudoprogression) in the intracranial metastases and any association with efficacy endpoints observed in the intracranial or extracranial compartment will be summarized by MRI-defined group (eg, edema, hemorrhage, pseudoprogression). If necessary, a comparison will be made between the MRI-defined event group and non-event group (eg presence of edema vs no edema).

[redacted]

[redacted]

Safety Analyses: Safety analyses will be summarized in all treated subjects by subgroup (prior to study with or without SRT and on study with or without SRT), overall and by cohorts (asymptomatic and symptomatic subjects). Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All treatment-emergent adverse events (AEs), drug-related AEs, serious adverse events (SAEs) and drug-related SAEs will be tabulated using worst grade per NCI CTCAE by system organ class and preferred term. On-study lab parameters including hematology, chemistry, liver function and renal function will be summarized using worst grade per NCI CTCAE criteria.

[redacted]

TABLE OF CONTENTS

[redacted]

1 INTRODUCTION [redacted]

[redacted]

1.2 Research Hypothesis

Treatment with nivolumab combined with ipilimumab, followed by nivolumab monotherapy, will provide clinical benefit to subjects with melanoma metastatic to the brain.

1.3 Objectives

Study objectives will be applied for all treated subjects (Cohort A and Cohort B).

Primary, secondary, and exploratory efficacy endpoints and safety analyses will be reported in the treated subjects, for overall population, by cohorts (asymptomatic and symptomatic), and by subgroup (prior to study with or without SRT and on study with or without SRT).

1.3.1 Primary Objective

Primary Objective: To assess intracranial clinical benefit rate (CBR, defined as complete response [CR] + partial response [PR] + stable disease [SD] $\geq$ 6 months) in subjects with melanoma metastatic to the brain per modified RECIST 1.1 criteria.

1.3.2 Secondary Objectives

- To assess the extracranial clinical benefit rate defined as CR+PR+SD > 6 months (per RECIST 1.1 criteria)
- To assess intracranial objective response rate (ORR), intracranial progression-free survival (PFS) per modified RECIST 1.1 criteria
- To assess extracranial ORR, extracranial PFS per RECIST 1.1 criteria
- To assess global CBR, global ORR, global PFS per a combination of modified RECIST 1.1 criteria for intracranial lesions and RECIST 1.1 for extracranial disease
- To assess OS
- To evaluate the intracranial-specific safety and tolerability of the combination regimen in patients with or without stereotactic radiotherapy (SRT) received prior to study entry, or while on study.

[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.

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

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

2.2 Institutional Review Board/Independent Ethics Committee

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

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

2.3 Informed Consent

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

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

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

Investigators must:

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

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

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

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

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

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is an open-label, multi-site Phase 2 study of nivolumab combined with ipilimumab followed by nivolumab monotherapy for the treatment of subjects with melanoma metastatic to the brain. Per Amendment 02 (August 2106), both asymptomatic and symptomatic patients are eligible for enrollment as described below:

Cohort A (asymptomatic) Patients with histologically confirmed metastatic melanoma presenting with intracranial metastases and at least 1 measurable index intracranial metastasis ≥ 0.5 cm and ≤ 3 cm in diameter that has not been previously irradiated. No clinical requirement for local intervention (surgery, radiosurgery, corticosteroid therapy) or other systemic therapy.

Approximate enrollment in Cohort A is 90 patients.

Cohort B (symptomatic): Patients with histologically confirmed metastatic melanoma presenting with symptomatic intracranial metastases who may be on steroids with doses no higher than a total daily dose of 4 mg of dexamethasone or equivalent that is stable or tapering within 10 days prior to treatment. Patients who are symptomatic and are not being treated with steroids are also eligible. Patients enrolled in Cohort B must have at least 1 measurable index intracranial metastasis ≥ 0.5 cm and ≤ 3 cm in diameter that has not been previously irradiated, must not require immediate local therapy (SRT or surgery within 3 weeks prior to first treatment), have a performance status 0-2, and no experience of seizure within 10 days prior to first treatment.

Approximate enrollment in Cohort B is 20 patients.

Asymptomatic subject who are enrolling into Cohort A and become symptomatic during the screening evaluations may be considered for enrollment into Cohort B if they meet all other criteria for Cohort B. No crossover between cohorts is permitted after the start of treatment.

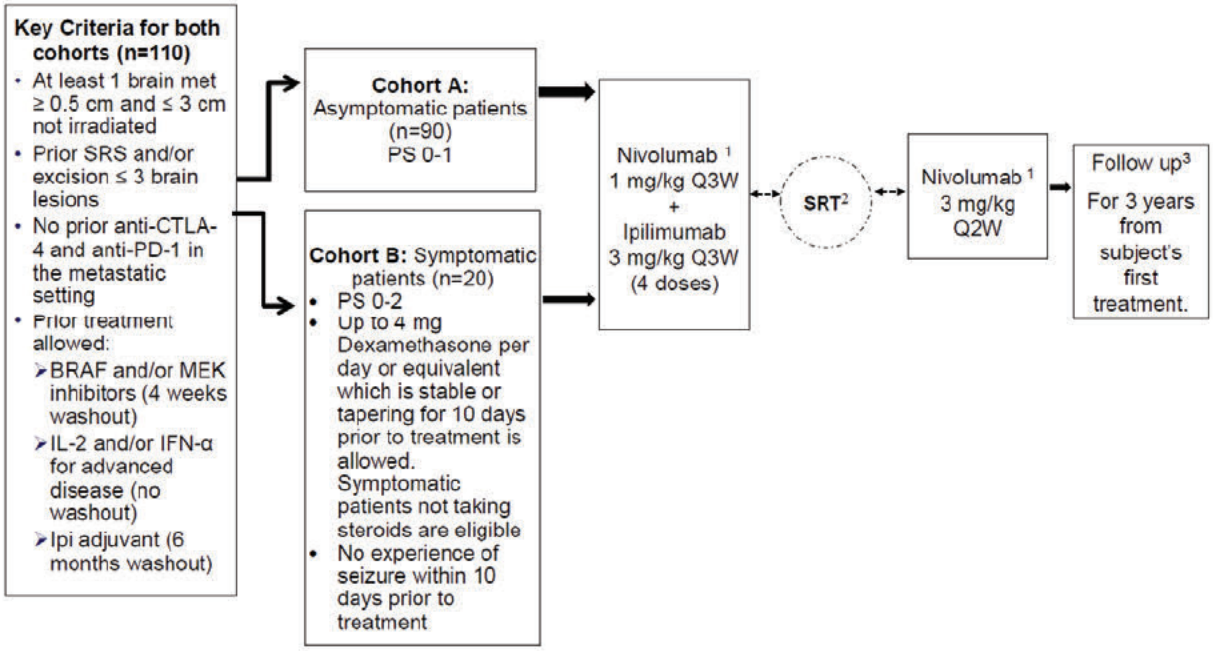
Subjects who have received prior treatment with BRAF inhibitors and/or MEK inhibitors, and subjects who have been treated with ipilimumab in an adjuvant setting are eligible for the study.

All patients will be treated with the combination regimen of nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg Q3W (4 doses), followed by nivolumab monotherapy (3 mg/kg Q2W) for a maximum of 24 months, or until disease progression or unacceptable toxicity. The use of SRT (single episode) for disease progression for ≤ 3 intracranial lesions is permitted. (Section 3.4.2.2) Recommended intervals between treatment with study drug and use of SRT, dose delay after SRT, allowable steroid use (≤ 16 mg dexamethasone PO QD), and tapered over no more than 4 weeks), and observation of patients post SRT when treatment is resumed are also specified in Section 3.4.2.2. Any subject who meets criteria for discontinuation following SRT (Section 4.5.5) will proceed to follow-up for safety, progression, and overall survival after discontinuation of study medication based on the assessment schedules presented in Section 5. NOTE: To continue on-study after SRT, at least 1 non-irradiated target lesion must remain after SRT treatment.

A follow-up period of 3 years from the date of first treatment with study drugs is available for all subjects. The study will close after the last enrolled subject completes 3 years of follow up from

the date of first treatment or the study is discontinued by the Sponsor. The study design is presented in Figure 3.1-1:

Figure 3.1-1: CA209204 Study Design



1 Subjects may continue to receive treatment for a maximum or 24 months, or until confirmed progression or unacceptable toxicity. After discontinuation from treatment with study drug(s) subjects will proceed to follow-up. Subjects who continue to respond at the end of on study treatment may be prescribed study medication through commercial supply or appropriate care per investigator.

2 Use of SRT for progression of ≤ 3 intracranial lesions will be allowed per protocol-specific guidelines (See Section 3.4.2.2). Subjects who require SRT after second episode of disease progression will be discontinued from treatment and proceed to follow-up.

3 All subjects who are discontinued from treatment with study drug(s) will proceed to follow-up. See Table 5.1-4 for schedule of follow up assessments.

SRT = stereotactic radiotherapy

Enrolled subjects will be evaluated for safety and efficacy throughout the study and during follow up at the time points indicated on the time and events schedules presented in Table 5.1-1, Table 5.1-2, Table 5.1-3, and Table 5.1-4. Response to treatment will be assessed in the intracranial and extracranial compartments and will be evaluated by serial radiographic assessment every 6 weeks for the first year and every 12 weeks thereafter until documented progression, withdrawal of consent, or the end of the study.

Follow-Up Phase for each enrolled subject begins when the decision to discontinue a subject from study therapy is made (no further treatment with study therapy). Subjects will be followed for efficacy and OS.

Treatment decisions will be based on local imaging evaluations using modified RECIST 1.1 for intracranial lesions (at least 5mm LD) and RECIST 1.1 for extracranial lesions (Appendix 3).

Additional imaging may be performed for patient care at the discretion of the investigator. All efficacy objectives will be based on Investigator assessment at the study site.

All radiologic imaging from this study will be transmitted to a centralized imaging core laboratory for storage and analysis. Sites will be informed of quality issues or the need for repeat scanning via queries from the core lab. The details of the independent review performed by the Independent Radiologic Review Committee (IRRC) are outlined in a separate CA209204 Imaging Review Charter.

Safety will be evaluated for all treated subjects using the NCI CTCAE version 4.0. Safety assessments will be based on medical review of AE reports, vital sign measurement results, physical examinations, and clinical laboratory tests. In addition, a designated Steering Committee composed of a core group of study investigators who are experts in treating patients with melanoma intracranial metastases and sponsor physicians/staff will evaluate safety and efficacy throughout the trial as described in Section 7.

[redacted]

Safety and Tolerability Assessment Evaluation of Risk/Benefit

An interim analysis was conducted when 20 subjects completed induction or discontinued treatment for any reason. At the completion of the interim analysis by the steering committee, the combination was determined to be safe in patients with asymptomatic untreated melanoma intracranial metastases. Per Amendment 02 (August 2016), the patient population will be expanded to include Cohort B, which will enroll approximately 20 patients with symptomatic intracranial metastases who may be on steroids provided there is no immediate need for SRT or surgery (within 3 weeks prior to first treatment, performance status is 0-2, the patient has not experienced seizure within 10 days prior to first treatment, and does not require steroid therapy at a total daily dose of higher than 4 mg of dexamethasone or equivalent, which is stable or tapering for 10 days prior to first treatment. Patients who are symptomatic and are not being treated with steroids for CNS symptoms are eligible for enrollment.

In the event unfavorable safety/tolerability event occurs in the interim analyses, the Steering Committee and the Sponsor will review the available data. Upon review of the risk/benefit profile, the Sponsor and the Steering Committee will recommend continuation, modification, or termination of the study.

The most frequent severe drug related AEs for the combination of nivolumab and ipilimumab in melanoma have been asymptomatic and reversible (eg, laboratory testing of liver function tests (LFT) and lipase levels) and preliminary evidence shows deep and durable responses in advanced melanoma (CA209004) despite these events. In particular, any assessment of the risk/benefit will be examined if the following criteria are met:

- A majority of subjects have at least stable disease or a partial tumor response

- All treatment-related AEs leading to discontinuation are non-fatal, reversible, and without severe sequelae
- A majority of the treatment related AEs are laboratory in nature, asymptomatic, and monitorable by routine blood draws.

If a decision is made to continue because of a favorable risk/benefit profile (ie, non-fatal AEs in subjects with at least stable disease or a partial tumor response) and despite meeting the safety signals for 'not tolerable' criteria, the EC/IRBs must be notified, Informed Consent forms updated if necessary to add new information, and discussion of the risk/benefit, if determined to be different than at the outset of the study, must be documented with all current and future subjects who are enrolled into the study.

3.1.1 Screening Phase

- Screening begins by establishing the subject's initial eligibility and signing of the ICF.
- Subject is enrolled using the IRT. Subjects will be enrolled into either Cohort A (asymptomatic) or Cohort B (symptomatic). Asymptomatic subjects who are enrolling into Cohort A and become symptomatic during the screening evaluations may be considered for enrollment into Cohort B if they meet all other criteria for Cohort B. No crossover between cohorts is permitted after the start of treatment.
- Subject is assessed for study eligibility as described in Section 3.3.1 and Section 3.3.2.
- Pre-treatment tumor tissue is required from all patients and should be from an excisional, incisional, (preferred), punch, or core needle biopsy. Tissue representing an extracranial metastasis collected after prior therapies is preferred, but archival primary or metastatic tumor tissue specimens are acceptable. A tumor tissue block or minimum of 15 slides should be submitted.

3.1.2 Treatment Phase

- A negative pregnancy test should be documented within 24 hours prior to start of each dose of investigational product.
- On study laboratory assessments should be drawn within 72 hours prior to dosing.
- Study assessments are to be collected as outlined in Table 5.1-2 (Cycles 1 and 2) and Table 5.1-3 (Cycles 3 and beyond).
- Adverse event assessments should be documented at each clinic visit.
- Outcomes Research Assessment (Healthcare Resources Utilization (HCRU) will be conducted prior to Cycle 1 dosing and at the time of progression.
- Exploratory Biomarker Testing will be conducted according to Table 5.6.1.3-1.
- All enrolled participants will be treated with nivolumab IV over 60 minutes ± 10 minutes at 1 mg/kg combined with ipilimumab administered IV over 90 minutes ± 10 minutes at 3 mg/kg every 3 weeks for a total of 4 doses of the combination therapy followed by nivolumab administered IV over 60 minutes ± 10 minutes at 3mg/kg every 2 weeks for a maximum of 24 months or until progression or unacceptable toxicity.

- Study drug dose may be delayed for toxicity. Tumor assessment should be continued as per protocol even if dosing is delayed.
- Response to treatment will be evaluated by serial radiographic assessment every 6 weeks (± 7 days) for the first 12 months and every 12 weeks (± 7 days) thereafter until documented progression.
- NANO Scale evaluation to be conducted weekly during Cycle 1, prior to dosing on Weeks 1 and 4 in Cycle 1 and Cycle 2; and on Weeks 1, 3, and 5 during Cycle 3 and thereafter during the treatment phase. See Section 8.4.3.1.
- The treatment phase ends when the subject is discontinued from study therapy. For a complete list of reasons for treatment discontinuation see Section 3.5.

3.1.3 Follow-Up Phase

- Begins when the decision to discontinue a subject from treatment is made (no further treatment with study therapy).
- After completion of the first two follow-up visits, subjects will be followed every 3 months for survival.
- Follow-up assessments are to be collected as outlined in Table 5.1-4.
- Subjects who discontinue treatment for reasons other than tumor progression will continue to have tumor assessments beginning 6 weeks (± 7 days) from the first dose of study drug for the first 12 months, and every 12 weeks (± 7 days) thereafter until documented tumor progression.
- Subjects will be followed for drug-related toxicities until these toxicities resolve, return to baseline or are deemed irreversible. All adverse events will be documented for a minimum of 100 days after last dose.

3.2 Post Study Access to Study Drug

At the end of the study, BMS will not continue to provide BMS supplied study drug to subjects/investigators unless BMS chooses to extend the study. The investigator should ensure that the subject receives appropriate care to treat the condition under study. Subjects who continue to respond at the end of on study treatment may be prescribed study medication through commercial supply.

3.3 Study Population.

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

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent
   a) Subjects must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal subject care.
   b) Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study.

2. Target Population

   a) Histologically confirmed malignant melanoma with measurable metastases in the brain

   b) **Cohort A**: At least 1 measurable intracranial metastasis ≥ 0.5 cm and ≤ 3 cm in longest diameter that has not been previously irradiated. No clinical requirement for local intervention (surgery, radiosurgery, corticosteroid therapy) or other systemic therapy.

      Cohort B: Per Amendment 02 (August 2016) Subjects with neurologic signs and symptoms related to metastatic intracranial lesions are eligible per Amendment 02. Subjects must have at least 1 measurable intracranial metastasis ≥ 0.5 cm and ≤ 3 cm in longest diameter that has not been previously irradiated. No immediate requirement (within 3 weeks prior to first treatment) for local intervention (surgery, radiosurgery, corticosteroid therapy). Steroid use is permitted as defined in inclusion criterion 2e).

   c) Prior stereotactic radiotherapy (SRT) and prior excision of up to 3 melanoma intracranial metastases is permitted if there has been complete recovery, with no neurologic sequelae, and measurable lesions remain. Growth or change in a lesion previously irradiated will not be considered measurable. Regrowth in cavity of previously excised lesion will not be considered measurable. Any prior SRT to intracranial lesions or prior excision must have occurred ≥ 3 weeks before the start of dosing for this study.

   d) Must have tumor tissue available for biomarker analysis. Biopsy should be excisional, incisional, punch, or core needle. Fine needle aspirates or other cytology samples are not allowable.

   e) **Cohort A** (asymptomatic): Subjects must be free of neurologic signs and symptoms related to metastatic intracranial lesions and must not have required or received systemic corticosteroid therapy within 10 days prior to first treatment.

      Cohort B (symptomatic): Subjects with neurologic signs and symptoms related to metastatic intracranial lesions are eligible per Amendment 02. Subjects with neurologic signs and symptoms may be treated with a total daily dose of no more than 4 mg of dexamethasone that is stable or tapering for 10 days prior to first treatment. Subjects with neurologic signs and symptoms who are not being treated with steroids are eligible for Cohort B. No experience of seizure within 10 days prior to first treatment.

   f) Allowable prior therapy

      i) Approved adjuvant therapies, which may include molecularly-targeted agents, IFN-α, and ipilimumab. Patients who received ipilimumab as adjuvant therapy must have a 6 month washout before receiving any dosing on this study

      ii) For advanced disease, interleukin-2 at any dose and/or IFN-α (any formulation, no washout required); MEK and BRAF inhibitors: washout for at least 4 weeks prior to the start of dosing in this study

      iii) Steroids for physiological replacement are allowed.

   g) Cohort A (asymptomatic): ECOG performance status ≤ 1.
      Cohort B: (symptomatic): ECOG performance status ≤ 2

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

- WBC ≥ 2000/uL
- Neutrophils ≥ 1500/uL
- ANC ≥ 1000/uL
- Platelets ≥ 100 x 10^3/uL
- Hemoglobin ≥ 9 g/dL
- Serum Creatinine ≤ 1.5 x ULN or calculated creatinine clearance > 40 mL/min (using the Cockcroft-Gault formula)

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

  Male CrCl = $\frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/ dL}}$
- AST ≤ 3.0 x ULN
- ALT ≤ 3.0 x ULN
- Total Bilirubin ≤ 1.5 x ULN, (except subjects with Gilbert's syndrome who must have a total bilirubin < 3.0 x ULN).

i) Subject Re-enrollment: This study permits the re-enrollment of a subject who has discontinued the study as a pre-treatment failure (ie, has not been treated) if the reason for pre-treatment failure is related to the size of potential index lesions. If re-enrolled, the subject must be re-consented.

3. Age and Reproductive Status

a) Males and Females, ≥18 years.

b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.

c) Women must not be breastfeeding.

d) Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception for a period of 30 days (duration of ovulatory cycle) plus the time required for the investigational drug to undergo approximately five half lives.

WOCBP should use an adequate method to avoid pregnancy for 23 weeks (30 days plus the time required for nivolumab to undergo five half-lives) after the last dose of investigational drug.

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for a period of 90 days (duration of sperm turnover) plus the time required for the investigational drug to undergo approximately five half lives.

Males who receive nivolumab who are sexually active with WOCBP must continue contraception for 31 weeks (90 days plus the time required for nivolumab to undergo five half-lives) after the last dose of investigational drug.

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

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

At a minimum, subjects must agree to the use of two methods of contraception, with one method being highly effective and the other method being either highly effective or less effective as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena® by WOCBP subject or male subject's WOCBP partner. Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug
- Nonhormonal IUDs, such as ParaGard®
- Tubal ligation
- Vasectomy.
- Sexual Abstinence
  - It is not necessary to use any other method of contraception when complete abstinence is elected.
  - WOCBP participants who choose complete abstinence must continue to have pregnancy tests.
  - Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence.

LESS EFFECTIVE METHODS OF CONTRACEPTION

- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge
- Male Condom without spermicide
- Progestin only pills by WOCBP subject or male subject's WOCBP partner
- Female Condom*.

* A male and female condom must not be used together

3.3.2 Exclusion Criteria

1) Target Disease Exceptions
   a) History of known leptomeningeal involvement (lumbar puncture not required).
   b) Previous stereotactic or highly conformal radiotherapy within 3 weeks before the start of dosing for this study. Note the stereotactic radiotherapy field must not have included the intracranial index lesion(s).
   c) Subjects previously treated with SRT > 3 lesions in the brain
   d) Intracranial lesion size > 3cm
2) Medical History and Concurrent Diseases
   a) History of whole brain irradiation.
   b) Subjects with an active, known or suspected autoimmune disease. Subjects with type I diabetes mellitis, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
   c) Subjects with major medical, neurologic or psychiatric condition who are judged as unable to fully comply with study therapy or assessments should not be enrolled.
   d) Any concurrent malignancy other than non-melanoma skin cancer or carcinoma in situ of the cervix. For any prior invasive malignancy, at least 5 years must have elapsed since curative therapy and patients must have no residual sequelae of prior therapy.
   e) **Cohort A**: (asymptomatic): The use of corticosteroids is not allowed within 10 days prior to first treatment (based upon 5 times the expected half-life of dexamethasone) except patients who are taking steroids for physiological replacement. If alternative corticosteroid therapy has been used, consultation with the sponsor Medical Monitor is required to determine the washout period prior to initiating study treatment.
   Cohort B: (symptomatic): Subjects with neurologic sign and symptoms related to intracranial metastases who are being treated with a total daily dose of **higher** than 4 mg dexamethasone or equivalent within 10 prior to the start of treatment with study drug are excluded.
   f) Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
   g) Subjects with history of life-threatening toxicity related to prior ipilimumab adjuvant therapy except those that are unlikely to re-occur with standard countermeasures (eg. hormone replacement after adrenal crisis).
3) Physical and Laboratory Test Findings
   g) Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic infection
   h) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS) even if fully immunocompetent on ART—

due to the unknown effects of HIV on the immune response to combined nivolumab plus ipilimumab or the unique toxicity spectrum of these drugs in patients with HIV.

4) Allergies and Adverse Drug Reaction
   a) History of allergy to study drug components.
   b) History of severe hypersensitivity reaction to any monoclonal antibody.
5) Other Exclusion Criteria
   i) Prisoners or subjects who are involuntarily incarcerated.
   j) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

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

3.3.3 Women of Childbearing Potential

A Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40mIU/mL to confirm menopause.

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

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

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

[redacted]

[redacted]

3.5 Discontinuation of Subjects from Treatment with Study Drugs

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

- Subject's request to stop study treatment
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Additional protocol specified reasons for discontinuation including the development of treatment-emergent, treatment-related unacceptable toxicity including neurological toxicity (see Section 4.5.5 and Section 4.5.5.1)

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

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

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

3.6 Post Study Drug Study Follow up

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

BMS may request that survival data be collected on all treated subjects outside of the protocol defined window (Table 5.1-4). At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contacts or is lost to follow-up.

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study drug will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, 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 Sponsor-retained

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

4 STUDY DRUG

Study drug includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) and can consist of the following (Table 4-1):

- All products, active or placebo, being tested or used as a comparator in a clinical trial.
- Study required premedication, and
- Other drugs administered as part of the study that are critical to claims of efficacy (eg, background therapy, rescue medications)
- Diagnostic agents: (such as glucose for glucose challenge) given as part of the protocol requirements must also be included in the dosing data collection.

Table 4-1: Study Drugs for CA209204

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
Nivolumab Solution for Injection	100 mg (10 mg/mL)	IP	Open-label	Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8° C. Protect from light, freezing and shaking.
Ipilimumab Solution for Injection	200 mg (5 mg/mL)	IP	Open-label	Clear, colorless to pale yellow liquid. May contain particles	2 to 8° C. Protect from light and freezing.

Premedications or medications used to treat infusion-related reactions should be sourced by the investigative sites if available and permitted by local regulations.

4.1 Investigational Product

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

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

In this protocol, investigational products are nivolumab and ipilimumab.

4.2 Non-investigational Product

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

4.3 Storage and Dispensing

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

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

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

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

Please refer to the current version of the nivolumab and ipilimumab IBs and/or pharmacy reference sheets for complete storage, handling, dispensing, and infusion information for BMS-936558 (nivolumab) and BMS-734016 (ipilimumab).

Nivolumab

Nivolumab vials must be stored at a temperature of 2° C to 8° C and should be protected from light, freezing, and shaking. 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.

For details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration, please refer to the nivolumab IB section for "Recommended Storage and Use Conditions" and/or pharmacy reference sheets. Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent. No incompatibilities between nivolumab and polyolefin bags have been observed.

Nivolumab is to be administered as a 60-minute IV infusion ± 10 minutes using a volumetric pump with a 0.2/0.22 micron in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% normal saline for delivery but the total drug concentration of the solution cannot be below 0.35 mg/ml. 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.

Ipilimumab

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

Ipilimumab is to be administered as a 90-minute IV infusion ± 10 minutes, using a volumetric pump with a 0.2 to 1.2 micron in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% normal saline or 5% Dextrose Injection to concentrations between 1 mg/mL and 4 mg/mL. It is not to be administered as an IV push or bolus injection. Care must be taken to assure sterility of the prepared solutions, since the drug product does not contain any antimicrobial preservatives or bacteriostatic agents.

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.

4.4 Method of Assigning Subject Identification

CA209204 study is an open-label study. After the subject's initial eligibility is established and informed consent has been obtained, the subject must be enrolled into the study by calling an interactive voice response system (IVRS) to obtain the subject number. Every subject that signs the informed consent form must be assigned a subject number in IVRS. Specific instructions for using IVRS will be provided to the investigational site in a separate document. The investigator or designee will register the subject for enrollment by following the enrollment procedures established by BMS. The following information is required for enrollment:

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

4.5 Selection and Timing of Dose for Each Subject.

All enrolled subjects will be treated in an open-label fashion as described below:

- Nivolumab administered IV over 60 minutes ± 10 minutes at 1 mg/kg combined with ipilimumab administered IV over 90 minutes ± 10 minutes at 3 mg/kg every 3 weeks for a total of 4 doses of the combination therapy followed by nivolumab administered IV over 60 minutes ± 10 minutes at 3mg/kg every 2 weeks for a maximum of 24 months or until progression or unacceptable toxicity.

Dosing schedule is detailed in Table 4.5-1 and Table 4.5-2 .

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Table 4.5-1: CA209204: Dosing Schedule for Cycle 1 and Cycle 2

1 Cycle = 6 weeks						
	Day 1 Week 1	Day 1 Week 2	Day 1 Week 3	Day 1 Week 4	Day 1 Week 5	Day 1 Week 6
All Enrolled Subjects Combination Treatment (Nivolumab 1mg/kg + Ipilimumab 3 mg/kg)	1 mg/kg Nivolumab + 3 mg/kg Ipilimumab			1 mg/kg Nivolumab + 3 mg/kg Ipilimumab		

Table 4.5-2: CA209204 Dosing Schedule Cycle 3 and Beyond

Subjects may continue to receive treatment for a maximum of 24 months from the Date of the First Treament with Nivolumab +Ipilimumab. **1 Cycle = 6 weeks**						
	Day 1 Week 1	Day 1 Week 2	Day 1 Week 3	Day 1 Week 4	Day 1 Week 5	Day 1 Week 6
All Enrolled Subjects Nivolumab monotherapy	3 mg/kg Nivolumab		3 mg/kg Nivolumab		3 mg/kg Nivolumab	

4.5.1 Antiemetic Premedications

Antiemetic premedications should not be routinely administered prior to dosing of drugs. See Section 4.5.6 for premedication recommendations following either a nivolumab- or an ipilimumab-related infusion reaction.

4.5.2 Dose Delay Criteria

Dose delay criteria apply for all drug-related adverse events (regardless of whether or not the event is attributed to nivolumab, ipilimumab, or both). All study drugs must be delayed until treatment can resume. See Section 4.5.4.

Ipilimumab and / or nivolumab administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related adverse event, with the following exceptions:
  - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
- Any Grade 3 skin, drug-related adverse event
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, AST, ALT, or total bilirubin or asymptomatic amylase or lipase:
  - Grade 3 lymphopenia does not require dose delay
  - If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity
  - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity
  - Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay. The BMS Medical Monitor should be consulted for such Grade ≥ 3 amylase or lipase abnormalities.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

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

Tumor assessments should continue as per protocol even if dosing is delayed.

4.5.2.1 SRT and Dose interruptions

If a patient requires SRT for a single episode of intracranial progression in ≤ 3 intracranial metastases, treatment with study drug will be interrupted as specified in Section 3.4.2.2. The protocol specified steroid treatment and taper (≤ 16 mg dexamethasone PO daily tapered in ≤ 4 weeks four week steroid) must be completed before treatment with the study drugs is resumed.

The length of dose delay/dose interruptions for patients receiving SRT is counted from the date of the last dose of study drug. As specified in Section 4.5.5, patients may resume treatment with study drug after the protocol allowed limit of 6 weeks, if approved by the BMS Medical Monitor. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks for any reason including on study treatment with SRT, the BMS Medical Monitor must be consulted.

If the patient is unable to resume treatment due to corticosteroid dependence or neurologic symptoms, the patient will discontinue study drug treatment and go to follow-up.

4.5.2.2 Resumption of Treatment after Dose Delay

If there is a delay in treatment due to AEs associated with study medication, when the patient resumes treatment, he/she will receive the next dose, rather than the missed dose. If the dose delay occurs during the combination treatment (induction), the patient will receive less than 4 doses of the combination treatment.

If there is a delay due to SRT or AEs not associated with study medication, when the patient resumes treatment, he/she will receive the missed dose. If the dose delay occurs during the combination treatment (induction), the patient has the opportunity to receive all four doses of the combination treatment.

4.5.3 Dose modifications

Dose reductions or dose escalations are not permitted.

4.5.4 Criteria to Resume Treatment

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

- Subjects may resume treatment in the presence of Grade 2 fatigue
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity

- Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 4.5.5) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the BMS Medical Monitor.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor

Dose delay of treatment that results in treatment interruption of > 6 weeks requires treatment discontinuation, with exceptions as noted in Section 4.5.2.1 and Section 4.5.5

There will be no dose reductions for study medications.

If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled time point per protocol. However, if the treatment is delayed past the next scheduled time point per protocol, the next scheduled time point will be delayed until dosing resumes.

- If treatment is delayed > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified in Section 4.5.2.1 and Section 4.5.5.

4.5.5 Discontinuation of Study Drug

Treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies::
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
- Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
  - AST or ALT > 8 x ULN

  - Total bilirubin > 5 x ULN
  - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia
  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis. The BMS Medical Monitor should be consulted for Grade 4 amylase or lipase abnormalities.
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
- Any event that leads to delay in dosing lasting > 6 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks from the previous dose, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.
  - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor. Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab or ipilimumab dosing.

Note: If a subject experiences a severe adverse event during induction treatment (ie, the combination of nivolumab and ipilimumab) that requires discontinuation from further treatment with the combination, continuing treatment with nivolumab monotherapy may be considered contingent on discussion with and approval by the BMS Medical Monitor.

Exceptions to Permanent Discontinuation of study drug dosing under the following situations:

- Potentially reversible inflammation (< Grade 4), attributable to a local anti-tumor reaction and a potential therapeutic response. This includes inflammatory reactions at sites of tumor resections or in draining lymph nodes, or at sites suspicious for, but not diagnostic of metastasis.
- Subjects with the following conditions where in the investigator's opinion continuing study drug administration is justified:
  - Endocrinopathies where clinical symptoms are controlled with appropriate hormone replacement therapy.

4.5.5.1 Discontinuation of Treatment with Study Drug due to Neurotoxicity

Treatment-related neurologic adverse events, ≥ Grade 3 define unacceptable neurotoxicity and require permanent discontinuation of study drug. Any neurologic adverse event that occurs at increased frequency or severity, or is unexpected in nature, should be considered potentially related to study treatment.

4.5.6 Treatment of Nivolumab or Ipilimumab Related Infusion Reactions

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

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

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

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

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

Stop the nivolumab or ipilimumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further BMS-936558 will be administered at that visit.

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

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

- Immediately discontinue infusion of nivolumab or ipilimumab. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the Investigator is comfortable that the symptoms will not recur. Nivolumab or ipilimumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms.

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

4.5.7 *Treatment Beyond Initial Radiological Assessment of Disease Progression*

As previously described in Section 1.1.2.4, accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[23] This phenomenon was observed in approximately 10% of subjects in the Phase 1 study of nivolumab and has also been reported for ipilimumab monotherapy.

Subjects receiving treatment in this study will be permitted to continue treatment beyond initial PD (intracranial metastases using modified RECIST 1.1 criteria; extracranial disease by RECIST 1.1) as long as they meet the following criteria:

- Investigator assesses clinical benefit AND
- Subject is tolerating study drug.

If a patient has disease progression of ≤ 3 intracranial lesions, the patient may receive SRT (single episode) as clinically appropriate and then resume study treatment as outlined in Section 3.4.2.2.

Subjects with confirmed progression (confirmation assessment will occur approximately 4 weeks after initially assessed progression) will be assessed radiographically and by clinical judgment as to whether the subject is deriving clinical benefit from treatment and should continue study treatment or discontinue and enter the follow up/survival phase of the study according to the time and events schedule presented in Section 5. If progression is confirmed, then the date of disease progression will be the first date the subject met the criteria for progression.

All decisions to continue treatment beyond initial progression must be discussed with the BMS Medical Monitor and documented in the study records. Subject must provide written informed consent prior to receiving additional nivolumab treatment. All other elements of the main consent

including description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply

For 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 the sum of diameters of all target lesions and/or the diameters of new measurable lesions compared to the time of initial PD. Treatment with study medication should be discontinued permanently upon documentation of further progression.

4.6 Blinding/Unblinding

Not applicable.

4.7 Treatment Compliance

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

4.8 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 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 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.

4.9 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 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.

Arrangements for the return of study drug will be made by the responsible Study Monitor.

[redacted]

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Assessments (CA209204)

Procedure	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening.
Medical History	X	
Tumor Tissue Samples	X	• Pre-treatment tumor tissue is required from all patients and should be from an excisional, incisional, (preferred), punch, or core needle biopsy. Tissue representing an extracranial metastasis collected after prior therapies is preferred, but archival primary or metastatic tumor tissue specimens are acceptable. A tumor tissue block or minimum of 15 slides should be submitted. • The following are optional: -H&E of primary cutaneous melanoma with accompanying pathology report; where available but strongly recommended (can be submitted at later date) -Intracranial metastasis: Any biopsy specimen acceptable (block or minimum of 15 slides); where available • -Submit a copy of the original pathology reports that correspond to submitted specimens if available.
Safety Assessments		
Complete Physical Examination	X	
Vital Signs and oxygen saturation	X	Including BP, HR, temperature, and oxygen saturation by pulse oximetry. Pulse oximetry at rest and after exertion. Obtain vital signs at the screening visit and within 72 hours prior to first dose
Physical Measurements	X	Height and weight
Performance Status	X	
ECOG	X	Within 14 days prior to dosing
Assessment of Signs and Symptoms	X	Within 14 days prior to dosing

Table 5.1-1: Screening Assessments (CA209204)		
Procedure	**Screening Visit**	**Notes**
[redacted]	[redacted]	[redacted]
Laboratory Tests	X	CBC w/differential, Chemistry panel including: LDH, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, Glucose, amylase, lipase, TSH, Free T4, Free T3, Hep B/C (HBV sAG, HCV antibody, or HCV RNA) within 14 days prior to dosing
Pregnancy Test (WOCBP Only)	X	Serum or urine must be performed.
Efficacy Assessments		
Tumor Assessment	X	Section 5.4 CT/MRI Chest, abdomen, pelvis and all known or suspected sites of disease within the prior 28 days. Brain MRI is required within the prior 14 days. Scans must follow sponsor-supplied Imaging Manual.

Table 5.1-2: On-study Assessments Cycles 1 and 2 Only (CA209204)

Procedure	Cycle 1 and Cycle 2 (Cycle = 6 weeks)						Notes • **Tumor assessment should be continued as per protocol even if dosing is delayed**
	Day 1 Week 1	**Day 1 Week 2**	**Day 1 Week 3**	**Day 1 Week 4**	**Day 1 Week 5**	**Day 1 Week 6**	
Safety Assessments							
Targeted Physical Examination Cycle 1	X	X	X	X	X	X	**Cycle 1**: **Weekly** for first 6 weeks: conducted by study physician; Within 72 hours prior to dosing on Weeks 1 and 4.
Cycle 2	X			X			**Cycle 2**: **Weeks 1 and 4**: conducted by study physician within 72 hours prior to dosing.
Phone assessment with study medical staff: Cycle 2 only.		X	X		X	X	**Cycle 2**: **Weeks 2,3,5,6** * Phone assessment with study medical staff required
Vital Signs and Oxygen Saturation Cycle 1	X	X	X	X	X	X	Including BP, HR, temperature, and oxygen saturation by pulse oximetry. Pulse oximetry at rest and after exertion prior to dosing. **Cycle 1**: Weekly for first 6 weeks.
Cycle 2	X			X			**Cycle 2**: Weeks 1 and 4 only
Physical Measurements (including performance status) Cycle 1	X	X	X	X	X	X	Weight and ECOG status within 72 hours prior to dosing. **Cycle 1**: Weekly for first 6 weeks.
Cycle 2	X			X			**Cycle 2**: Weeks 1 and 4 only
Adverse Events Assessment	Continuously						
[redacted]	[redacted]						[redacted]
[redacted]	[redacted]						[redacted]

Table 5.1-2: On-study Assessments Cycles 1 and 2 Only (CA209204)

Procedure	Cycle 1 and Cycle 2 (Cycle = 6 weeks)						Notes • Tumor assessment should be continued as per protocol even if dosing is delayed
	Day 1 Week 1	Day 1 Week 2	Day 1 Week 3	Day 1 Week 4	Day 1 Week 5	Day 1 Week 6	
Laboratory Tests	X			X			Within 72 hrs prior to dosing to include CBC w/differential, LFTs, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, Glucose, amylase, lipase, TSH (with reflexive Free T4 and Free T3)
Pregnancy Test (WOCBP Only)	X			X			Within 24 hours prior to administration of study drug. Serum or Urine
[redacted]	[redacted]						[redacted]
[redacted]							[redacted]
[redacted]			[redacted]				[redacted]
[redacted]			[redacted]				[redacted]
[redacted]			[redacted]				[redacted]
[redacted]			[redacted]				[redacted]
[redacted]			[redacted]				[redacted]

Table 5.1-2: On-study Assessments Cycles 1 and 2 Only (CA209204)

Procedure	Cycle 1 and Cycle 2 (Cycle = 6 weeks)						Notes
	Day 1 Week 1	Day 1 Week 2	Day 1 Week 3	Day 1 Week 4	Day 1 Week 5	Day 1 Week 6	• **Tumor assessment should be continued as per protocol even if dosing is delayed**
Efficacy Assessments							
Tumor Assessment	Section 5.4 **CT/MRI of chest, abdomen, pelvis, and brain (MRI).** **FIRST** tumor assessment should first be performed at 6 weeks (± 7 days) from first dose date. **SUBSEQUENT** tumor assessments should occur every 6 weeks (± 7 days) up to first 12 months (week 48), then every 12 weeks (±7 days) until documented disease progression.						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]			[redacted]			[redacted]
Administer Study Treatment							
Nivolumab 1mg/kg + Ipilimumab 3 mg/kg	X			X			Dose will remain the same as long as current patient weight is within 10% of the Cycle 1/Day 1/enrollment weight Doses may be administered within 2 days after the scheduled date if necessary. See Section 4.5.2.1 for dose interruption specific for SRT.

Table 5.1-3: On-study Assessments Cycle 3 and Beyond (CA209204)

Procedure	Cycle 3 and Beyond (Cycle = 6 weeks)						Notes
	Day 1 Week 1	Day 1 Week 2	Day 1 Week 3	Day 1 Week 4	Day 1 Week 5	Day 1 Week 6	• **Tumor assessment should be continued as per protocol even if dosing is delayed.** • **Subjects may continue to receive treatment for a maximum of 24 months from the Date of the First Treatment with Nivolumab +Ipilimumab.**
Safety Assessments							
Targeted Physical Examination	X		X*		X		Week 1 and Week 5: conducted by study physician. *Week 3: conducted by study medical staff. May be performed more frequently 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 prior to dosing.
Physical Measurements and Performance Status	X		X		X		Weight and ECOG status within 72 hours prior to dosing.
Adverse Event Assessment	Continuously						
[redacted]	[redacted]		[redacted]		[redacted]		[redacted]
Laboratory Tests	X				X		Within 72 hrs prior to dosing to include CBC w/differential, LFTs, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, Glucose, amylase, lipase, TSH (with reflexive Free T4 and Free T3)
Pregnancy Test (WOCBP Only)	X				X		Within 24 hours prior to administration of study drug. Serum or Urine
[redacted]	[redacted]						[redacted]

Table 5.1-3: On-study Assessments Cycle 3 and Beyond (CA209204)

Procedure	Cycle 3 and Beyond (Cycle = 6 weeks)						Notes
	Day 1 Week 1	Day 1 Week 2	Day 1 Week 3	Day 1 Week 4	Day 1 Week 5	Day 1 Week 6	• Tumor assessment should be continued as per protocol even if dosing is delayed. • Subjects may continue to receive treatment for a maximum of 24 months from the Date of the First Treatment with Nivolumab +Ipilimumab.
[redacted]							[redacted]
[redacted]			[redacted]				[redacted]
[redacted]			[redacted]				[redacted]
Efficacy Assessments							
Tumor Assessments	Section 5.4 **CT/MRI of chest, abdomen, pelvis, and brain (MRI).** **FIRST** tumor assessment should first be performed at 6 weeks (± 7 days) from first dose date. **SUBSEQUENT** tumor assessments should occur every 6 weeks (± 7 days) up to first 12 months (week 48), then every 12 weeks (±7 days) until documented disease progression.						
[redacted]	[redacted]		[redacted]		[redacted]		[redacted]

Table 5.1-3: On-study Assessments Cycle 3 and Beyond (CA209204)

Procedure	Cycle 3 and Beyond (Cycle = 6 weeks)						Notes
	Day 1 Week 1	Day 1 Week 2	Day 1 Week 3	Day 1 Week 4	Day 1 Week 5	Day 1 Week 6	• **Tumor assessment should be continued as per protocol even if dosing is delayed.** • **Subjects may continue to receive treatment for a maximum of 24 months from the Date of the First Treatment with Nivolumab +Ipilimumab.**
Administer Study Treatment							
Nivolumab 3 mg/kg	X		X		X		Dose will remain the same as long as current patient weight is within 10% of the Cycle 1/Day 1/enrollment weight Doses may be administered within 2 days after the scheduled date if necessary. Subjects may continue to receive treatment for a maximum of 24 months from the Date of the First Treatment with Nivolumab +Ipilimumab

Table 5.1-4: Follow-up Assessments (CA209204)

Procedure	Follow-Up[a] Visits 1 and 2	Survival[b] Follow-up Visits	Notes Follow up is 3 years from start of treatment.
Safety Assessments			
Complete Physical Examination	X		To assess for potential late emergent study drug related issues
Adverse Events Assessment	X	X	All SAEs must be collected that occur within 100 days of the last dose of study drug(s). All nonserious adverse events (not only those deemed to be treatment-related) should be collected for a minimum of 100 days following discontinuation of study treatment. Every adverse event must be assessed by the investigator with regard to whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information will be collected on the subject's case report form.
Laboratory Tests	X		Perform Lab tests for Follow-up Visit 1 and repeat at Follow-up Visit 2, if any study drug toxicity persists. CBC w/differential, LFTs, BUN or serum urea level, creatinine, glucose, amylase, lipase, TSH (with reflexive Free T4 and Free T3).
Pregnancy Test (WOCBP Only)	X		Serum or urine
[redacted]	[redacted]		[redacted]
Document any current treatment regimen	X	X	To include immuno-therapy, chemotherapy, targeted therapy, radiotherapy, surgery, and all interventions to treat metastatic melanoma.
Survival Status		X	
Subject Status	X	X	Every 3 months, may be accomplished by visit or phone contact, to include subsequent anti-cancer therapy
[redacted]	[redacted]		[redacted]

Table 5.1-4: Follow-up Assessments (CA209204)			
Procedure	**Follow-Up[a] Visits 1 and 2**	**Survival[b] Follow-up Visits**	**Notes Follow up is 3 years from start of treatment.**
Efficacy Assessments			
Tumor Assessments	X		Only for subjects who have not progressed on study therapy or who have discontinued study treatment for reasons other than documented disease progression. Section 5.4 **CT/MRI of chest, abdomen, pelvis and brain (MRI)** **FIRST** tumor assessment should first be performed at 6 weeks (± 7 days) from first dose date. **SUBSEQUENT** tumor assessments should occur every 6 weeks (± 7 days) up to first 12 months (week 48), then every 12 weeks (±7 days) until documented disease progression.
[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]

[a] Follow-up Visit 1 = 30 days from the last dose +/- 7 days or coincide with the date of discontinuation (+/- 7 days) if date of discontinuation is greater than 37 days after last dose, Follow-up visit 2 = 84 days (+/- 7 days) from follow-up visit 1

[b] Survival visits = every 3 months from Follow-up Visit 2 +/- 7 days

5.1.1 Retesting During Screening or Lead-in Period

Retesting of laboratory parameters and/or other assessments during the Screening or Lead-in period will not be permitted (this does not include parameters that require a confirmatory result) unless there was a technical error in performance of the lab test and the first result is invalid.

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

5.2 Study Materials

- NCI CTCAE version 4.0
- Nivolumab Investigator Brochure
- Ipilimumab Investigator Brochure
- Pharmacy Binder
- Laboratory manuals for collection and handling of blood (including biomarker) and tissue specimens
- Site manual for operation of interactive voice response system, including enrollment worksheets
- Pregnancy Surveillance Forms
- RECIST 1.1 pocket guide
- CA209204 Imaging Manual

5.3 Safety Assessments

5.3.1 Medical History, Physical Exam, Physical Measurements

At baseline, a medical history will be obtained to capture relevant underlying conditions. The baseline examinations should include weight, height, ECOG Performance Status, blood pressure (BP), heart rate (HR), temperature, and oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable) should be performed within 28 days prior to first dose.

Baseline local laboratory assessments should be done within 14 day prior to first dose and are to include: CBC w/differential, Chemistry panel including: LDH, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, Glucose, amylase, lipase, TSH, Free T4, Free T3, Hep B/C (HBV sAG, HCV antibody, or HCV RNA).

While on-study and during follow-up, local laboratory assessments are to be conducted as specified on Table 5.1-2 to Table 5.1-4. Thyroid function testing is to be done every 6 weeks (every 3 cycles) for subjects receiving nivolumab.

Subjects will be evaluated for safety if they have received any study drug. Toxicity assessments will be continuous during the treatment phase. During study treatment and nivolumab Follow-Up Visits 1 and 2, toxicity assessments should be done in person. Once subjects reach the survival follow-up, either in-person visits or documented telephone calls/email correspondence to assess the subject's status are acceptable.

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

Oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable) should be assessed at each on-study visit prior to dosing. The start and stop time of the study therapy infusions should be documented.

Physical examinations are to be performed as specified in Section 5.1 and as clinically indicated. If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate non-serious or serious adverse event page.

On treatment local laboratory assessments are to be completed within 72 hours prior to dosing.

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

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

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

5.3.2 Vital Signs

Vital signs consist of blood pressure, heart rate, respiratory rate and temperature measurements. Vital signs will be obtained as outlined in Table 5.1-1 to Table 5.1-3.

5.3.3 Imaging Assessment for the Study

All subjects will undergo CT scanning and volumetric MRI of the brain at the time points specified in Table 5.1-1 to Table 5.1-4.

CT and MRI scans will be assessed locally per the modified RECIST 1.1 criteria outlined in Appendix 3. Up to 5 extracranial and 5 intracranial lesions will be followed for efficacy per the criteria. Please refer to Appendix 3 for guidelines regarding images, target lesion selection and response criteria.

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

Clinically significant radiologic findings or changes from baseline scans will be coded as adverse events or serious adverse events according to the criteria described in Section 6.

5.3.4 Pregnancy Testing

WOCBP are required to have several pregnancy tests performed as presented in Table 5.1-1 to Table 5.1-4. A negative serum or urine pregnancy test must be documented at the screening visit as per Table 5.1-1. Additionally WOCBP must exhibit a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug; therefore the screening pregnancy test may need to be repeated prior to the start of study drug dosing. A serum or urine pregnancy test will also be conducted at End of Treatment Visit.

5.3.5 ECOG Status

ECOG performance status will be evaluated at the screening evaluation and at each visit as outlined in Time and E. An outline of the ECOG performance status is provided in Appendix 2.

5.3.6 Adverse Event Monitoring

Adverse Events (AEs) will be evaluated according to the NCI CTCAE Version 4.0 on a continuous basis starting from when the subject takes the first dose of study administration, up to and including Follow-Up and End of Treatment visits (at minimum, for 100 days following last dose of study drug). Serious Adverse Events (SAEs) must be collected from the time period following written consent to participate in the study up to and including follow-up.

5.3.7 Laboratory Test Assessments

Results of all safety laboratory collections must be obtained and reviewed in advance of study drug dosing, as applicable. Amylase and lipase should be collected with the chemistry collection, but these lab results do not require review prior to dosing.

Serum Chemistry is to be obtained as specified in Table 5.1-1 to Table 5.1-4. A free-T4 and free-T3 will be performed reflexively for out of range TSH values. A CBC with differential is to be obtained. The CBC with differential includes hemoglobin, hematocrit, white blood cells, platelets (direct platelet count), erythrocyte sedimentation rate, WBC differential enumeration of total and percentage of neutrophils, lymphocytes, eosinophils, basophils and monocytes.

5.4 Efficacy Assessments

Assessment of extracranial disease (by CT scan or other approved modalities and intracranial disease (by MRI scan) will be performed per the schedule in Table 5.1-1 to Table 5.1-4. Investigators may obtain more frequent follow-up MRI scans as medically indicated.

Baseline assessments should be performed within 28 days prior to first dose of study drug utilizing CT or MRI for systemic lesions and within 14 days for brain lesions (MRI only). In addition to chest, abdomen, pelvis, and brain, all known sites of disease should be assessed at baseline. Subsequent assessments should include chest, abdomen, pelvis, brain, and all known sites of disease and should use the same imaging method as was used at baseline. Subjects will be evaluated for tumor response beginning at 6 weeks (± 7 days) from the first dose of study drugs for the first 12 months and every 12 weeks (± 7 days) thereafter, until disease progression is documented or treatment is discontinued (whichever occurs later). Tumor assessments for ongoing

study treatment decisions will be completed by the investigator using RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 criteria for all systemic lesions and modified RECIST 1.1 for brain lesions (Appendix 3).

Radiographic images will be collected and sent to a centralized imaging core laboratory for storage and potential future central reading.

All radiologic imaging from this study will be assessed at the study site by the Investigator. Sites will be trained in image acquisition parameters, image analyses, and submission process, prior to scanning the first study subject. These guidelines will be outlined in a separate CA209204 Site Imaging Manual.

For extracranial disease assessment, contrast-enhanced computed tomography (CT) scans acquired on dedicated CT equipment is preferred for this study. CT with contrast of the chest, abdomen and pelvis and other areas of disease are to be performed for tumor assessments per Table 5.1-1 to Table 5.1-4. Should a subject have a contraindication for CT IV contrast, a non-contrast CT of the chest and a contrast enhanced MRI of the abdomen and pelvis may be obtained. MRI's should be acquired with slice thickness of $\leq$ 5 mm with no gap (contiguous).

Use of CT component of a PET/CT scanner: Combined modality scanning such as with FDG-PET/CT is increasingly used in clinical care, and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change rather quickly with time. At present, low dose or attenuation correction CT portions of a combined FDG-PET/CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically based RECIST measurements. However, if a site can document that the CT performed as part of a FDG-PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the FDG-PET/CT can be used for RECIST 1.1 measurements. Note, however, that the FDG-PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

MRI scans: Bi-dimensional and three-dimensional contrast enhanced MRI of the brain will be acquired per the CA209204 Imaging Manual requirements. Every attempt should be made to image each subject using an identical acquisition protocol on the same scanner for all imaging time points. Cases of suspected radiologic disease progression will be confirmed by an MRI performed approximately 4 weeks after the initial radiological assessment of progression.

5.4.1 Computed Tomography Imaging (CT)

Baseline CT assessments should be performed within 28 days prior to enrollment. In addition to chest, abdomen, pelvis, all known sites of disease should be assessed at baseline.

Subsequent CT assessments should occur at +/- 7 days per scheduled visits and should include chest, abdomen, and pelvis, and all known sites of disease. The same imaging method used at baseline should be used for all CT assessments. Subjects will be evaluated for tumor response every 6 weeks for Year 1 and every 12 weeks thereafter until progression or discontinuation, whichever is later.

5.4.2 Brain Magnetic Resonance Imaging (MRI)

All subjects will receive efficacy assessments with brain MRI at time points specified in Table 5.1-1 to Table 5.1-4. Baseline brain MRI should be performed with 14 days prior to enrollment.

All MRIs should occur at ± 7 days per scheduled visits. Investigators may obtain more frequent follow-up MRI scans as medically indicated.

5.4.3 Confirmation of Scans

Verification of Response: Confirmation of intracranial response will be confirmed by an MRI performed approximately 4 weeks after the initial radiological assessment. If repeat scans confirm overall response (OR), then response should be declared using the date of the initial scan. If repeat scans do not confirm OR, then the subject is considered not to have had an OR.

Verification of Progression: Progression of disease should be verified in cases where progression is equivocal and will be confirmed by an MRI performed approximately 4 weeks after the initial radiological assessment of progression. If repeat scans confirm PD, then progression should be declared using the date of the initial scan. If repeat scans do not confirm PD, then the subject is considered not to have progressive disease.

5.4.4 Algorithms for Response Assessments

5.4.4.1 Primary Efficacy Assessment

The primary endpoint of the study is intracranial CBR $\geq$ 6 months in subjects with malignant melanoma with intracranial metastases treated with nivolumab combined with ipilimumab therapy. Tumor response will be based on Investigator assessment using modified RECIST 1.1.

5.4.4.2 Secondary Efficacy Assessments

The secondary efficacy endpoints include extracranial CBR $\geq$ 6 months using RECIST 1.1 and will be based on Investigator assessment.

Additional secondary endpoints are specified in Section 8.4.2.

[redacted]

5.8 Results of Central Assessments

All radiologic imaging from this study will be transmitted to a centralized imaging core laboratory for storage and analysis. Sites will be informed of quality issues or the need for repeat scanning via queries from the core lab. The details of the independent review conducted by the Independent Radiologic Review Committee (IRRC) are outlined in a separate CA209204 Imaging Review Charter.

All efficacy objectives will be evaluated by Investigator assessment based on local radiologic tumor measurements using a modified RECIST 1.1 for intracranial and RESCIST 1.1 for extracranial (Appendix 3).

6 ADVERSE EVENTS

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

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

Related: There is a reasonable causal relationship between study drug administration and the AE.

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

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

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

6.1 Serious Adverse Events

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

- results in death

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

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

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

NOTE:

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

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

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the IB represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs

must be collected that occur during the screening period and within 100 days of discontinuation of dosing.

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

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

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship 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). The preferred method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: See Contact Information list.

For studies capturing SAEs 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): Refer to Contact Information list.

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

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

All SAEs should be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

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

6.2.1 Nonserious Adverse Event Collection and Reporting

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

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause

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

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

6.3 Laboratory Test Result Abnormalities

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

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

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

6.4 Pregnancy

If, following initiation of the study drug, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half lives after product administration, the investigator must immediately notify the 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.

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours and in accordance with SAE reporting procedures described in Section 6.1.1.

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

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

6.5 Overdose

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

6.6 Potential Drug Induced Liver Injury (DILI)

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

Potential drug induced liver injury is defined as:

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

AND

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

AND

3) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

6.7 Other Safety Considerations

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

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

A Data Monitoring Committee external to BMS will not be used in this study. A Steering Committee will be created and composed of a core group of study investigators who are experts in treating patients with melanoma brain metastases with sponsor physicians/ study staff. The steering committee will be informed if a safety signal emerges and will be informed of the results of the interim analyses. After review of the available safety and tolerability data from the interim analysis, the Steering Committee will recommend continuation, modification or termination of the study.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

The total sample size for the treatment of nivolumab combined with ipilimumab is 110 subjects. All patients will contribute to the primary efficacy assessment.

Cohort A will enroll asymptomatic subjects (n ~ 90), and Cohort B will enroll symptomatic subjects (defined in Section 3.3.1).

Table 8.1-1 presents the clinical benefit rates (CBRs) that would have to be observed to yield clinically meaningful results with respect to the lower bounds of the Clopper-Pearson exact two sided 90% and 95% CI. The planned sample size ensures that the maximum width of the exact 90% CI for any given CBR estimate does not exceed 18% and the maximum width of the exact 95% CI for any given CBR estimate does not exceed 20%.

Table 8.1-1: CA209204: Clinical Benefit Rates – two sided 90% confidence interval (Clopper-Pearson)

		Nivolumab + Ipilimumab (n=110)		
	Clinically meaningful CBR	Observed CBR	Clopper-Pearson exact two-side 90% CI	Clopper-Pearson exact two-side 95% CI
Brain (intracranial)	40%	53/110 (48.2%)	(40.0%, 56.4%)	(38.5%, 57.9%)
		57/110 (51.8%)	(43.6%, 60.0%)	(42.1%, 61.5%)
Systemic (extracranial)/ Global (intracranial +extracranial)	50%	65/110 (59.1%)	(50.8%, 67.0%)	(49.3%, 68.4%)

CBR = Clinical Benefit Rate

If the observed intracranial CBR rate is 51.8%, the sample size of 110 will achieve 80.4% power to detect a difference of 11.8% (51.8% versus 40% historical intracranial CBR rate) with a type I error rate of 0.10 for the two-sided binomial test.

8.2 Populations for Analysis

- All Enrolled Subjects: All subjects who signed an informed consent form and were registered into the IVRS
- All Treated Subjects: All subjects who received at least one dose of any study medication.

[redacted]

8.3 Endpoint Definitions

8.3.1 Tumor Assessment Endpoints

8.3.1.1 Best Overall Response (BOR) per Subject

The best overall response is determined once all the data for the subject is known. It is defined as the best response designation, as determined by the investigator, recorded between the date of first dose of study drug and the date of objectively documented progression or the date of subsequent therapy, whichever occurs first. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR assessment.

In this study, BOR is specified for the intracranial, extracranial, and global compartments based on the (1) modified RECIST 1.1 criteria (intracranial), (2) RECIST 1.1 criteria (extracranial), (3) combination of modified RECIST 1.1 criteria and RECIST 1.1 criteria (global). Image assessment criteria (modified RECIST 1.1 and RECIST 1.1) are presented in Appendix 3.

For the assessment of BOR, all available assessments per subject are considered.

The best overall response for each patient is determined from the sequence of overall (lesion) responses according to the following rules, listed in order of priority:

- CR = At least two determinations of CR at least 4 weeks apart before progression.
- PR = At least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR).
- SD = At least one SD assessment ≥ 6 months after start of treatment.
- PD = At least two determinations of PD at least 4 weeks apart after start of treatment (and not qualifying for CR, PR or SD).

The BOR for each patient will also be determined by the IRRC as specified within the CA209204 Imaging Review Charter.

8.3.1.2 Overall Survival

Overall Survival (OS) is defined as the time from the date of the start of treatment until the date of death. For those subjects who have not died, OS will be censored at the recorded last date of subject contact, and subjects with a missing recorded last date of contact will be censored at the last date the subject was known to be alive.

8.4 Endpoints

8.4.1 Primary Endpoint

Intracranial clinical benefit rate (CBR) defined as the proportion of patients, whose best overall response according to modified RECIST1.1, is either complete response (CR), a partial response (PR) or stable disease (SD).

The primary endpoint is intracranial CBR. It is defined as the proportion of all treated subjects whose best overall response is either a CR or PR or whose best overall response was SD with duration of ≥6 months, as determined by modified RECIST 1.1 criteria for index intracranial lesions based on investigator review.

8.4.2 Secondary Endpoint(s)

Secondary endpoints are as follows:

- Intracranial ORR and intracranial PFS per modified RECIST 1.1 criteria;
- Extracranial CBR, extracranial ORR, extracranial PFS per RECIST 1.1 criteria

- Global (intracranial + extracranial) CBR, global ORR, and global PFS per a combination of modified RECIST 1.1 criteria for intracranial lesions and RECIST 1.1 for extracranial disease
- OS
- Safety and tolerability will be measured by the incidence of AE adverse events, serious adverse events (SAE), deaths, and laboratory abnormalities.

Overall survival (OS) is defined as the time from first dosing date to the date of death, will be estimated using the Kaplan-Meier product-limit method, with subjects censored at their last known date alive.

Progression-free survival (PFS) is defined as the time between the date of first dose of study drug and the first date of documented confirmed progression, as determined by the investigator, or death due to any cause, whichever occurs first. Subjects who die without a reported progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on study tumor assessments and did not die will be censored on the date of first dose of study drug. Subjects who started anti-cancer therapy without a prior reported progression will be censored on the date of their last evaluable tumor assessment prior to the initiation of subsequent anti-cancer therapy.

Overall response rate (ORR) is defined as the number of subjects who achieve a best overall response of complete response (CR) or partial response (PR) divided by the number of treated subjects. The best overall response is defined as the best response designation recorded between the date of first study dosing date and the date of progression, or the date of subsequent anticancer therapy (including tumor-directed radiotherapy and tumor-directed surgery), whichever occurs first.

Safety and tolerability will be measured by the incidence of adverse events, serious adverse events, deaths, and laboratory abnormalities.

[redacted]

[redacted]

[redacted]

8.5 Analyses

The analyses of primary, secondary, [redacted]).

8.5.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics for all treated subjects. Patients will be categorized into 4 groups according to their SRT status (prior to study with or without SRT and on study with or without SRT). Number of enrolled subjects will be summarized. Summarization will be provided for the overall group. by cohort (asymptomatic and symptomatic), and by subgroup (prior to study with or without SRT and on study with or without SRT).

8.5.2 Primary Efficacy Analyses

The primary endpoint of intracranial CBR will be calculated for the overall population and by cohorts (asymptomatic and symptomatic) with its corresponding two sided 90% exact CI using the Clopper-Pearson method. The two-sided 95% CI will also be calculated. A sensitivity analysis using IRRC-assessed intracranial CBR will also be performed.

In addition, a sensitivity analysis will also be conducted to evaluate the impact of SRT on intracranial CBR by excluding the patients who received on-study SRT.

8.5.3 Secondary Efficacy Analyses

For all the secondary efficacy analysis endpoints for the overall population and by cohorts (asymptomatic and symptomatic), a two-sided type I error rate 0.05 will be applied (including calculation of the confidence interval).

The secondary endpoints CBR (extracranial and global) and ORR (intracranial, extracranial and global) and corresponding 95% exact CIs will be calculated using the Clopper-Pearson method. BOR will be tabulated.

Time to event distributions (PFS [intracranial, extracranial and global] and OS,) will be estimated using Kaplan Meier methodology. When appropriate, the median along with 95% CI will be estimated based on Brookmeyer and Crowley methodology[63] (using log-log transformation for

constructing the confidence intervals). Rates at fixed time points (eg, OS at 12 months) will be derived from the Kaplan Meier estimate along with their corresponding log-log transformed 95% confidence intervals. Confidence intervals for binomial proportions will be derived using the Clopper-Pearson method.

In addition, sensitivity analyses using IRRC-assessed CBR (extracranial and global) and ORR (intracranial, extracranial, and global) will also be performed.

To estimate the incidence of MRI-defined intracranial edema, hemorrhage, and increase before regression (pseudoprogression) in the intracranial metastases and evaluate any association with the onset and/or duration of tumor response observed in the intracranial or system, efficacy results (CBR, OS, etc) will be summarized by MRI-defined groups. If necessary, comparisons will be made between MRI- defined event groups and non-event groups.

[redacted]

8.5.5 Safety Analyses

Subjects will be evaluated for safety if they have received any treatment for the overall population and by cohorts (asymptomatic and symptomatic). Adverse events and other symptoms will be graded according to National Cancer Institute's Common Toxicity Criteria for Adverse Events

version 4.0 (CTCAE v4). Additionally, serious adverse events (SAE) will be reported from the time of consent forward for all subjects. The analysis of safety will be based on the frequency of AEs and their severity for all treated subjects. Worst toxicity grades per subject will be used in the summary for AEs and laboratory measurements by using the CTCAE v4.

Safety analyses will be summarized in all treated subjects by subgroup (prior to study with or without SRT and on study with or without SRT) and for the overall population. All treatment emergent AEs, drug-related AEs, SAEs and drug-related SAEs will be tabulated using worst grade per NCI CTCAE by system organ class and preferred term. On-study lab parameters including hematology, chemistry, liver function and renal function will be summarized using worst grade per NCI CTCAE criteria.

[redacted]

8.5.9 Interim Analyses

To assess safety and tolerability, an interim analysis was conducted after 20 subjects completed induction treatment or discontinued treatment for any reason. At the completion of the interim analysis by the steering committee, the study drug treatment was deemed safe in asymptomatic patients. Per Amendment 02 (August 2016), the patient population was expanded to include Cohort B which will enroll approximately 20 symptomatic patients as specified in Section 3.3.1.

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
- BMS
- Regulatory Authority(ies), if required by local regulations

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

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

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

9.1.2 Monitoring

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

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

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

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

9.1.2.1 Source Documentation

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

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

9.1.3 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 BMS, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

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

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

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of study drug (inventoried and dispensed) is maintained at the study site to include investigational product and the following non-investigational product(s): ipilimumab. Records or logs must comply with applicable regulations and guidelines and should include:

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

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

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated

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

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

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

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

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

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

9.3 Clinical Study Report and Publications

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

For this protocol, the Signatory Investigator will be selected as appropriate based on the following criteria:

- External Principal Investigator designated at protocol development.

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study require approval by BMS prior to publication or presentation and must adhere to BMS'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 BMS 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. BMS 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
Complete Abstinence	If one form of contraception is required, Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. If two forms of contraception is required, Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. Expanded definition Complete abstinence as defined as complete avoidance of heterosexual intercourse is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (eg, calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence

11 LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
AI	accumulation index
AI_AUC	AUC Accumulation Index; ratio of AUC(TAU) at steady state to AUC(TAU) after the first dose
AI_Cmax	Cmax Accumulation Index; ratio of Cmax at steady state to Cmax after the first dose
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	area under the concentration-time curve
A-V	atrioventricular
β-HCG	beta-human chorionic gonadotrophin
BMI	body mass index
BMS	Bristol-Myers Squibb
BP	blood pressure
C	Celsius
C12	concentration at 12 hours
C24	concentration at 24 hours
Ca++	calcium
CBC	complete blood count
CBR	Clinical benefit ratio
CFR	Code of Federal Regulations
CI	confidence interval
C1-	chloride
CLcr	creatinine clearance
CLR	renal clearance
CLT	total body clearance

Term	Definition
cm	centimeter
Cmax, CMAX	maximum observed concentration
Cmin, CMIN	trough observed concentration
CNS	Central nervous system
CRF	Case Report Form, paper or electronic
Ctrough	Trough observed plasma concentration
CV	coefficient of variation
CYP	cytochrome p-450
D/C	discontinue
dL	deciliter
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEG	electroencephalogram
eg	exempli gratia (for example)
ESR	Expedited Safety Report
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
g	gram
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GFR	glomerular filtration rate
h	hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCO3-	bicarbonate
HIV	Human Immunodeficiency Virus
HR	heart rate
HRT	hormone replacement therapy

Term	Definition
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
IRB	Institutional Review Board
IU	International Unit
IV	intravenous
K+	potassium
kg	kilogram
L	liter
LD	longest dimension
LDH	lactate dehydrogenase
ln	natural logarithm
mg	milligram
Mg++	magnesium
MIC	minimum inhibitory concentration
min	minute
mL	milliliter
mmHg	millimeters of mercury
MS	mass spectrometry
MTD	maximum tolerated dose
µg	microgram
N	number of subjects or observations
Na+	sodium
N/A	not applicable
ng	nanogram
NIMP	non-investigational medicinal products
NSAID	nonsteroidal anti-inflammatory drug

Term	Definition
OS	Overall survival
PD	pharmacodynamics
PK	pharmacokinetics
PO	per os (by mouth route of administration)
PT	prothrombin time
PTT	partial thromboplastin time
QC	quality control
QD, qd	quaque die, once daily
RBC	red blood cell
SAE	serious adverse event
SD	standard deviation
SOP	Standard Operating Procedures
sp.	species
Subj	subject
t	temperature
T	time
TID, tid	ter in die, three times a day
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
x g	times gravity

APPENDIX 2 ECOG

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

[redacted]