Official Title of Study:

A MULTI-CENTER PHASE II 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

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STATISTICAL ANALYSIS PLAN FOR

A MULTI-CENTER PHASE II 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

VERSION # 2.3

TABLE OF CONTENTS

DOCUMENT HISTORY

Version Number	Date	[redacted]	Description
0.1	8Sep2015		Initial version
0.2	18Sep2015		Updated with BMS Stats comments
0.3	16Oct2015		Updated with BMS Medical comments and PPD 2nd Senior review
0.4	4Nov2015		Added HCRU analyses per BMS' recommendation.
1.0	12Nov2015		Cleaned up all review tracking markers. Removed "Disease Stage and M Status of initial diagnosis from list of baseline subject characteristics, for they were not collected by CRF.
1.1	2Mar2016		Dose intensity formula in Table 2 was modified per BMS Statistician's confirmation on 3/1/2016.
2.0	15May2017		Updated per Protocol Amendment 02
2.1	26Apr2018		Updated per Protocol Amendment 03
2.2	03Jul2018		Updated in line with DPP [redacted]. Updated sensitivity analysis to the primary efficacy endpoint to add 90%CI, and updated OESI per client request. Updated IMAEs per client request.
2.3	03Dec2020		Document history: Additional clarification of the reasoning for the update of section 4.1 on 23Apr2020. Section 1: Added information about eligibility for enrollment of symptomatic subjects. Section 3.1 and 4.1: Time period of SD is corrected to ≥6 months. Section 4.1: Added clarification of subsequent anti-cancer therapy. Section 4.2: Overall survival (OS) is added to the list of secondary endpoints Section 7.5.1: Added methodology for CRB based on BOR as reported on CRF. Section 7.5.5.2: Added clarification for concordance tables. Appendix 1: Updated Table 11-3 - Select Adverse Events Minor editorial corrections.

TABLE 1: ABBREVIATION

AE	Adverse Event
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
BICR	Blinded Independent Central Review
BMS	Bristol-Myers Squibb
BMI	Body Mass Index
BOR	Best Overall Response
BUN	Blood Urea Nitrogen
CBR	Clinical Benefit Rate
CI	Confidence Interval
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report Form, Paper or Electronic
CSR	Clinical Study Report
CTC	Common Toxicity Criteria
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eg	Exempli Gratia (for example)
HBV sAG	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCRU	Healthcare Resource Utilization
HCV	Hepatitis C Virus
HCV RNA	Hepatitis C Virus Ribonucleic Acid
ie	Id Est (That Is)
IV	Intravenous
IVRS	Interactive Voice Response System
kg	Kilogram
LDH	Lactate Dehydrogenase
MDSC	Myeloid-Derived Suppressor Cells
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram

MRI	Magnetic Resonance Imaging
N	Number of Subjects or Observations
NANO	Neurologic Assessment in Neuro-Oncology
NCI CTCAE	National Cancer Institute's Common Toxicity Criteria for Adverse Events
NSCLC	Non-small Cell Lung Cancer
OS	Overall Survival
ORR	Objective Response Rate
PD	Progressive Disease
PFS	Progression Free Survival
PO	Per os (by mouth route of administration)
PPD	Pharmaceutical Product Development, LLC
PR	Partial Response
PT	Preferred Terms
Q2W	Every 2 Weeks
Q3W	Every 3 Weeks
QD	Quaque Die, Once Daily
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SOC	System Organ Class
SRT	Stereotactic Radiotherapy
TSH	Thyroid-stimulating Hormone
TTR	Time to Objective Response
ULN	Upper Limit Normal
UTD	Unable to Determine
WHO	World Health Organization

[redacted]

[redacted]

Research Hypothesis:

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

Schedule of Analyses:

The first interim analysis was conducted after 20 subjects have completed induction treatment or have been discontinued due to an Adverse Event (AE) or progression after treatment with at least one dose of combination treatment.

After the first interim safety analysis conducted 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 that will enroll approximately 20 patients.

The final analysis will be performed following the data base lock after all subjects have completed the study. Study schedules are detailed in protocol Section 5.1.

2 STUDY DESCRIPTION

2.1 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 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. Per Amendment 02, August 2016, the patient population was expanded to include Cohort B, which will enroll approximately 20 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 for Cohort B. 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. 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 with a history of whole brain irradiation are not eligible for this study.

All patients will be treated with the combination regimen of nivolumab 1 mg/kg combined with ipilimumab 3mg/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 or withdrawal of consent.

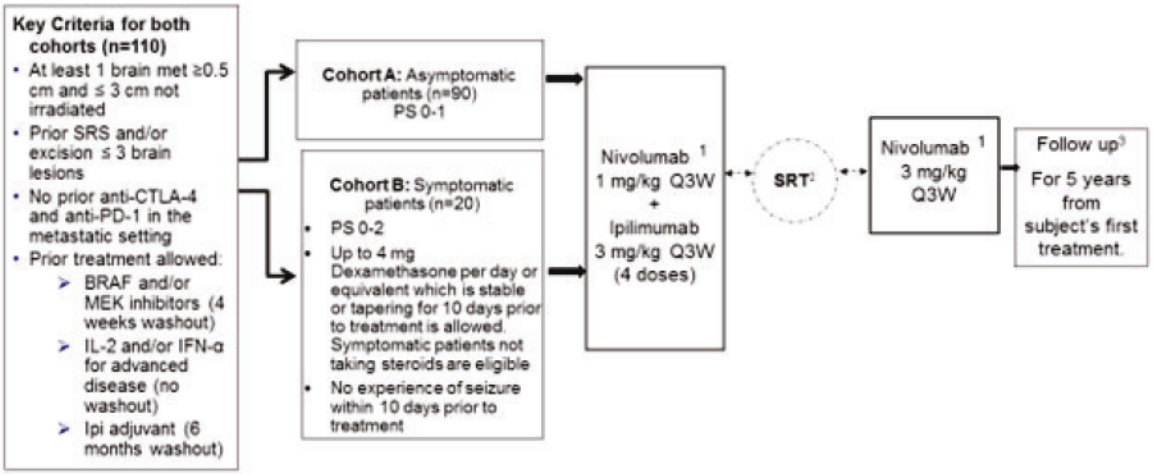
The combination induction regimen of nivolumab and ipilimumab followed by nivolumab maintenance monotherapy proposed for this study is based on safety and tolerability data from the use of nivolumab and ipilimumab in systemic metastatic melanoma and other tumor types (Protocol Section 1.4.3) and the proposed treatment regimen is expected to be tolerable in subjects with melanoma metastatic to the brain.

The use of SRT for a single episode of disease progression for ≤ 3 intracranial lesions is permitted (Protocol 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 (Protocol Section 4.5.5) will proceed to follow-up for safety, progression, and overall survival (OS) after discontinuation of study medication based on the assessment schedules presented in Protocol Section 5.

To assess safety and tolerability as well as efficacy, one interim analysis was conducted for this study after 20 subjects completed induction treatment or had discontinued treatment for any reason. At the completion of the interim analysis by the steering committee, the study drug treatment was deemed as safe in asymptomatic patients. A second cohort of patients who are symptomatic will be enrolled per Amendment 02 (August 2016). The study will close after the last enrolled subject completes 5 years of follow up from the date of first treatment.

The study design schematic is presented in Figure 1.

Figure 1: Study Design Schematic



1 Subjects may continue to receive 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 appropriate standard of 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 received a maximum of 24 months of treatment will proceed to follow-up.

This study will consist of three phases: screening, treatment, and follow-up. And the treatment phase has two parts: Part I – Induction, Part II – Maintenance.

2.2 Treatment Assignment

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.

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.

- Dose reductions or dose escalations are not permitted.
- Dose can be delayed 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.
- If treatment is delayed > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified in protocol Section 4.5.2.1 and Section 4.5.5.
- 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 protocol 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.

2.3 Protocol Amendments

Global Amendment 03 (See Protocol Document History).

3 OBJECTIVES

Study objectives will be applied for all 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 SRT status (prior to study with or without SRT and on study with or without SRT).

3.1 Primary Objective

The primary objective of this study is to assess intracranial clinical benefit rate (CBR, defined as complete response [CR] + partial response [PR] + stable disease [SD] ≥ 6 months) in subjects with melanoma metastatic to the brain per modified RECIST 1.1 criteria.

3.2 Secondary Objective

The secondary objectives of this study are:

- 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 SRT received prior to study entry, or while on study

[redacted]

4 ENDPOINTS

4.1 Primary Endpoints

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

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). Best response determination in trials where confirmation of complete or partial response is required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in protocol Appendix 3. There is no confirmation requirement for progressive disease (PD). The BOR for each patient as determined by the BICR is determined from a predefined set of rules specified within the Image Review Charter.

To ensure the accuracy of primary endpoints, analyses will be based on two sets of BOR: BOR as reported in the CRF and BOR with adjustment. BOR as reported in the CRF uses information entered in the CRF directly by investigators without adjustment. Results based on BOR with adjustments will serve as primary analysis. This decision was made after the interim database lock on 09August2020.

BOR with adjustment uses information entered in the CRF with the following adjustments:

- If BOR is NE, and the radiographic progression date is non-missing and prior to subsequent anti-cancer therapy start date, or subsequent anti-cancer therapy start date is missing, change BOR to PD.

- If BOR is SD, and the radiographic progression date is non-missing and duration of SD is less than 6 months and radiographic progression date is prior to subsequent anti-cancer therapy start date, or subsequent anti-cancer therapy start date is missing, change BOR to PD.

- If BOR is PR or CR, and there is preceding (confirmed or unconfirmed) PD and
    - if the radiographic progression date is prior to or equal to the minimum of complete response date and partial response date, change BOR to PD;
    - if BOR is CR and both the complete response date and partial response date are non-missing and radiographic progression date is between those two, change BOR to PR.

4.2 Secondary Endpoints

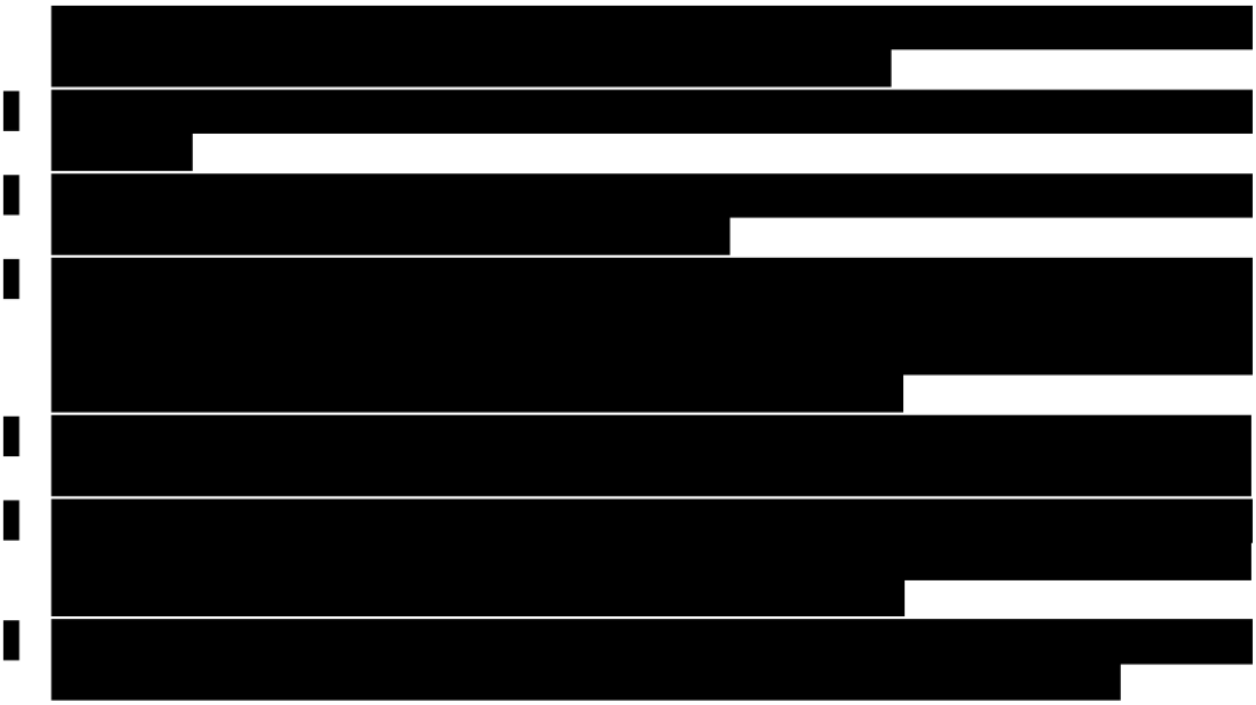
- Intracranial objective response rate (ORR) and intracranial progression free survival (PFS) per modified RECIST 1.1 criteria.
- Extracranial CBR, extracranial ORR, extracranial PFS per RECIST 1.1 criteria
- Global (intracranial +extracranial) CBR, global ORR, and global PFS per a combination of modified 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 AEs, serious adverse events (SAE), deaths, and laboratory abnormalities.

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.

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

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



5 SAMPLE SIZE AND POWER

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 (n ~ 20).

Table 5-1: 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	40%	53/110 (48.2%)	(40.0%, 56.4%)	(38.5%, 57.9%)
(intracranial)		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%)

Table 5-1 presents the 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% confidence interval (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%.

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.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

6.1.1 Baseline period

Baseline evaluations or events will be defined as the last non-missing evaluation or event that occurs before the date and time of the first dose of study treatment.

In cases where the time (onset time of event or evaluation time and dosing time) is missing or not collected, the following definitions will apply:

- Baseline evaluations (laboratory tests and vital signs) will be defined as evaluations with a date on or prior to the day of first dose of study treatment in part I.

If there are multiple valid pre-treatment assessments, the assessment that is closest to the day (and time if collected) of the first dose of study treatment in part I will be used as the baseline in the analyses.

- Pre-treatment AEs will be defined as AEs with an onset date prior to but not including the day of the first dose of study treatment in part I.

If there are multiple valid pre-treatment assessments, the assessment that is closest to the day (and time if collected) of the first dose of study treatment will be used as the baseline in the analyses. If multiple assessments are collected at the same date (and time if collected), the assessment with the latest database entry date (and time if collected) will considered as baseline.

If more than one tumor biopsy specimen is available, baseline PD-L1 expression will be determined from the most recently collected specimen (prior to first dose of study treatment) with a measurable result. If all specimens for a given subject are either indeterminate or unknown, then the PD-L1 expression will be considered indeterminate as long as at least one specimen is indeterminate. Otherwise, PD-L1 expression will be considered unknown.

6.1.2 On study period

On-study evaluations (laboratory tests and vital signs) will be defined as evaluations taken after the day (and time, if collected and not missing) of first dose of study treatment. For subjects who are off study treatment, evaluations should be within 100 days of the last dose of study treatment.

On-study AEs will be defined as AEs with an onset date-time on or after the date-time of the first dose of study treatment in part I (or with an onset date on or after the day of first dose of study treatment if time is not collected or is missing). For subjects who are off study treatment, AEs will

be counted as on-study if they occurred within 30 days (or 100 days depending on the analysis) of the last dose of study treatment.

Late emergent drug-related AEs will be defined as drug-related AEs with an onset date greater than 100 days after the last dose of study treatment in subjects off study treatment.

6.2 Treatment Regimens

All enrolled subjects will be treated in an open-label fashion with the combination regimen 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.
- Nivolumab Injection (100 mg/10 mL [10 mg/mL] and 40 mg/mL [10 mg/mL]) is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding polyethersulfone membrane in-line filter at the protocol-specified doses. No IV push or bolus injection is allowed. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 1 mg/mL. Instructions for dilution and infusion of nivolumab injection may be provided in the clinical protocol, pharmacy binder, or pharmacy reference sheet. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

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

6.3 Analysis Populations

- 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 study therapy.
- Intracranial response evaluable subjects: All treated subjects who have CR, PR, SD or PD as intracranial BOR, have baseline and at least one valid post-baseline intracranial target lesion assessments.
- Extracranial response evaluable subjects: All treated subjects who have CR, PR, SD or PD as extracranial BOR, have baseline and at least one valid post-baseline extracranial target lesion assessments.
- Global response evaluable subjects: All treated subjects who have CR, PR, SD or PD as global BOR, have baseline and at least one valid post-baseline global target lesion assessments.
- Subjects Treated Beyond Progression: Subjects with last available dose after initial progression date.

[redacted]

7 STATISTICAL ANALYSES

SAS® version 9.2 or higher will be used for statistical analyses, tabulations and graphical presentations.

7.1 General Methods

Descriptive summaries will be presented for continuous variables using number of subjects (N), mean, standard deviation, median, minimum and maximum. Descriptive summaries for categorical variables will utilize counts and percentages. Corresponding by-subject listings will also be created for appropriate populations.

Time to event distributions (i.e. progression free survival, overall survival, time to response, and duration of response) will be estimated using Kaplan Meier techniques. When appropriate, the median along with 95% CI will be estimated based on Brookmeyer and Crowley methodology[1] (using log-log transformation for constructing the confidence intervals). Rates at fixed timepoints (e.g. 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.

AEs and medical history will be coded according to the most recent Medical Dictionary for Regulatory Activities (MedDRA). Previous and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary.

7.1.1 Adverse Events, Serious Adverse Events, Multiple events and Select Adverse Events

Drug-related AEs are those events with relationship to study drug "Related", as recorded on the CRF. If the relationship to study drug is missing, the AE will be considered as drug-related.

Serious adverse events consist of AEs deemed serious by the Investigator and flagged accordingly in the CRF and clinical database.

Adverse events leading to study drug discontinuation are AEs with action taken = "Drug was discontinued".

Adverse events leading to dose delay are AEs with action taken = "Dose was delayed".

Adverse events leading to dose reduction are AEs with action taken = "Dose was reduced".

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and the most recent version of the dictionary at the time of the database lock will be used. Adverse events results will be graded for severity using NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 criteria.

In the AE summary tables, unless otherwise specified, subjects will be counted only once at the Preferred Term (PT), only once at the System Organ Class (SOC), and only once at subject level

for the counting of total number of subjects with an AE. The AE tables will list the SOCs (ordered by descending frequency) and the PTs (ordered by descending frequency within each SOC).

Unless otherwise specified, the AE summary tables will be restricted to on-treatment events regardless of the causality.

Analyses that take into account the multiple occurrences of a given adverse event will be conducted (see Section 7.6.8). To prepare these analyses, the CRF data will be processed according to standard BMS algorithms in order to collapse adverse event records into unique records based on the preferred term. This data will be presented as the rate per 100 person-years of exposure. These analyses will take into account all on-treatment events (allowing more than 1 event per subject) and the total exposure time. The person-year exposure will be computed as the sum over the subjects' exposure expressed in years where the exposure time is defined as

- Date of last dose of study treatment - date of first dose of study treatment +31 days (or 101 days, depending on the analysis), for subject who are off study treatment and were followed for at least 30 days (or 100 days, depending on the analysis) after last dose of study treatment.
- Last known date alive- date of first dose of study treatment +1, for subjects who are still on-treatment or who are off study treatment and were followed less than 30 days (or 100 days depending on the analysis) after last dose of study treatment.

When specified the 95% CI of the rate per 100 person-year of exposure will be derived using normal approximation and variance estimation proposed in Cook and Lawless.

7.1.1.1 Select Adverse Events

The select Adverse Events (select AEs) consist of a list of preferred terms grouped by specific category (e.g. pulmonary events, gastrointestinal events categories, etc.). AEs that may differ from or be more severe than AEs caused by non-immunotherapies and AEs whose early recognition and management may mitigate severe toxicity are included as select AEs. The select AEs and the categories are defined by the Sponsor and the list that is the most current at the time of analysis will be used. Changes may be made to this list with each new version of MedDRA prior to database lock. Categories of select AEs may include subcategories (e.g. adrenal disorders, diabetes, pituitary disorders, and thyroid disorders are subcategories of the endocrine event category).

In addition to the frequency and worst severity of select AEs, time-to onset, time-to resolution, and time-to resolution where immune modulating medication was initiated will be analyzed for each specific category/subcategory when applicable.

The list of MedDRA preferred terms used to identify select adverse events is revisited quarterly and updated accordingly. The preferred terms used for the selection at the time of the database lock will be provided by categories/sub-categories.

Further details on the definitions of select adverse event, time-to onset and time-to resolution are described in APPENDIX 1.

7.1.2 Laboratory Tests

Clinical laboratory parameters (hematology, serum chemistry and electrolytes) will be evaluated.

Laboratory tests will be graded using the NCI Common Terminology Criteria, version 4.0. Clinical laboratory data will be first analyzed using International System of Units (SI). Analyses will be repeated using US conventional units.

7.2 Study Conduct

7.2.1 Accrual

The accrual pattern will be summarized per country, investigational site, and per month for all treated subjects. The summaries will be repeated by cohorts and by SRT status.

First dosing date, country, investigational site will be presented in a by subject listing of accrual.

7.2.2 Relevant Protocol Deviations

The following programmable deviations will be considered as relevant protocol deviations and summarized for all treated subjects overall and by cohorts. Non-programmable relevant eligibility and on-treatment protocol deviations, as well as significant (both programmable and non-programmable) eligibility and on-treatment protocol deviations will be reported through ClinSIGHT listings.

At Entrance:

- For Cohort A, Subjects with baseline ECOG performance status > 1. For Cohort B, Subjects with baseline ECOG performance status > 2
- Subjects who received prior systemic anti-cancer treatment in the metastatic setting excluding 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
- Subjects without histologically documented Stage IV melanoma, as per AJCC staging system

On-study:

- Subjects receiving anti-cancer therapy (chemotherapy, hormonal therapy, immunotherapy, standard or investigational agents for treatment of cancer) while on study therapy. The use of SRT for a single episode of disease progression for ≤ 3 intracranial lesions is permitted (Protocol Section 3.4.2.2)

Listings will also be provided.

7.3 Study Population

Summaries of study population will be based on all treated subjects, except that of subject disposition which will be based on all enrolled subjects.

7.3.1 Subject Disposition

Summaries of subject disposition will be repeated by cohorts (asymptomatic and symptomatic) and by SRT status.

All enrolled subjects will be summarized by treated or not treated, with the number and percentage of subjects.

Disposition of all treated subjects will be summarized by the following categories: subjects who completed Induction, subjects who completed Maintenance, subjects who completed study treatment, subjects who discontinued study treatment, and subjects who completed the study.

The reasons for discontinuation of study treatment will also be summarized. The reason for discontinuation of study treatment may include any of the following: lack of efficacy, AE, subject request, death, lost to follow up, poor / noncompliance, pregnancy, subject no longer meets study criteria, administrative reason by sponsor, study drug toxicity, disease progression, and other.

The reasons for discontinuation of study participation will also be summarized. The reason for discontinuation of study participation may include any of the following: lack of efficacy, AE, subject request, death, lost to follow up, poor / noncompliance, pregnancy, subject no longer meets study criteria, administrative reason by sponsor, study drug toxicity, disease progression, and other.

The number of subjects and percentage of each category will be based on the all treated subjects population.

Subject disposition data will also be presented in a by-subject listing.

7.3.2 Demographics and Baseline Characteristics

A summary of demographics and baseline information will be summarized using descriptive statistics. The number and percentage of subjects by categories will be based on the total number of treated subjects.

The demographic characteristics:

- Age (years), which will be calculated as follows: Age = maximum integer ≤ ([Date of informed consent – Date of Birth +1] / 365.25)
- Age category I (<65, >= 65)
- Age category II (<65, >= 65-<75, >=75)
- Gender (Male, Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and Other)
- Ethnicity (Hispanic/Latino, Not Hispanic/Latino)

The baseline characteristics:

- Weight (kg)
- ECOG PS (0,1) for Cohort A; ECOG PS (0,1,2) for Cohort B
- LDH category I (<=ULN, >ULN)
- LDH category II (<=2*ULN, >2*ULN)
- M-stage at study entry (M0, M1A, M1B, M1C))
- BRAF mutation status (Mutation, Wild Type)
- NRAS mutation status (Mutation, Wild Type)
- BRAF/NRAS mutation status (Yes, No)

- SRT status prior to study entry (Yes, No)
- Number of prior SRT (0, 1, 2, >=3)
- Investigator Tumor Assessments at Baseline: Sites of disease, number of disease sites per subject presence of target lesions, presence of non-target lesions, site of target lesion, sum of longest diameter of target lesion, number of target lesion and number of non-target lesions, for intracranial, extracranial and global assessments.
- Blinded Independent Central Review (BICR) Tumor Assessments at Baseline: Sites of disease, number of disease sites per subject, presence of target lesions, presence of non-target lesions, site of target lesion, sum of longest diameter of target lesion, number of target lesions and number of non-target lesions, for intracranial, extracranial and global assessments.
- Disease Stage at Study Entry (Stage IV) - disease staging was determined by AJCC7.
- PD-L1 Status (<1% vs >=1%, <5% vs >=5%, <10% vs >=10%, INDETERMINATE/NOT EVALUABLE)

Summaries of demographic characteristics will be repeated by cohorts and by SRT status. Investigator tumor assessments at baseline will be repeated by dexamethasone subgroups for Cohort B (subjects who received prior dexamethasone vs not received prior dexamethasone). All demographic and baseline characteristics data will be listed.

7.3.3 Medical History and Previous Treatment

General medical history will be listed by subject for all treated subjects.

7.3.4 Prior Cancer Therapy

The following will be summarized for all treated subjects, by cohorts and SRT status.

- Prior adjuvant therapy (Yes, No)
- Time from completion of prior adjuvant therapy to treated (subjects who received prior adjuvant therapy), (< 6 months and > = 6 months)
- Prior surgery related to cancer (Yes, No)
- Prior radiotherapy (Yes, No)
- Prior regimen received by setting (adjuvant, metastatic)
- Agents and medication will be reported using the generic name. Listings by subject will also be provided.

7.3.5 Baseline Physical Examination

Subjects with abnormal baseline physical exam results will be tabulated by examination criteria (e.g., neck, cardiovascular, lungs, etc.) for all treated subjects and by cohorts and SRT status, and listed for all treated subjects.

7.4 Extent of Exposure

Analyses in this section will be performed in all treated subjects. All of the summary tables will be repeated for all treated subjects, by cohorts and by SRT status.

7.4.1 Administration of Study Therapy

The following parameters will be summarized (descriptive statistics) for all treated subjects, by cohorts and by SRT status:

- Number of concomitant doses received (A subject will be considered to have received concomitant doses of nivolumab and ipilimumab if both infusions are administered on the same date)
- Duration of study therapy

The following parameters will be summarized (descriptive statistics) by study therapy (nivolumab and ipilimumab) and study phase (induction, maintenance and overall) for all treated subjects, by cohorts and by SRT status:

- Relative dose intensity (%) using the following categories: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110% (Note: This will be presented by study phase only and not overall).
- Number of doses received (summary statistics)
- Cumulative dose
- Duration of treatment: will be presented using a Kaplan-Meier curve whereby the last dose date will be the event date for subjects who are off study therapy. Median duration of treatment and associated 95% CI will be provided. Subjects who are still on study therapy will be censored on their last dose date.

A by-subject listing of extent of exposure: weight, number of doses, date of first and last dose, cumulative dose, relative dose intensity, duration of treatment, and reason for discontinuation will be provided. A by-subject listing of dosing of study medication (record of study medication, infusion details, and dose changes) and a listing of batch numbers will be also provided.

Table 2: Administration of study therapy: definition of parameters

	Part I
Dosing schedule per protocol	1 mg/kg nivolumab + 3mg/kg ipilimumab every 3 weeks for 4 cycles
Dose	Dose (mg/kg) is defined as Total Dose administered (mg)/Most recent weight (kg). Dose administered in mg at each dosing date and weight are collected on the CRF.
Cumulative Dose	Cum dose (mg/kg) is sum of the doses (mg/kg) administered to a subject during the treatment period.
Relative dose intensity (%)	Cum dose (mg/kg) /[(Last dose date of induction - Start dose date + 21) /21] x 100, for nivolumab Cum dose (mg/kg) /[(Last dose date of induction - Start dose date + 21) x 3/21] x 100, for ipilimumab
Duration of treatment	Last dose date of induction - Start dose date +1
	Part II
Dosing schedule per protocol	3 mg/kg nivolumab every 2 weeks in part 2 until progression or a maximum of 48 weeks, whichever comes first

	Part I
Dose	Dose (mg/kg) is defined as Total Dose administered (mg)/Most recent weight (kg). Dose administered in mg at each dosing date and weight are collected on the CRF.
Cumulative Dose	Cum dose (mg/kg) is sum of the doses (mg/kg) administered to a subject during the treatment period.
Relative dose intensity (%)	Cum dose (mg/kg) /[(Last dose date - Start dose date of maintenance + 14) x 3/14] x 100
Duration of treatment	Last dose date - Start dose date of maintenance +1

7.4.2 Modifications of Study Therapy

7.4.2.1 Dose Delays

Each nivolumab and ipilimumab infusion may be delayed. A dose will be considered as actually delayed if the delay is exceeding 3 days (i.e. greater than or equal to 4 days from scheduled dosing date) for both nivolumab and ipilimumab. All studies drugs must be delayed until treatment can resume. Reason for dose delay will be retrieved from CRF dosing pages.

- The following parameters will be summarized bystudy therapy (nivolumab and ipilimumab) for all treated subjects, and by cohort and SRT status:
- Number of dose delays per subject, length of delay, and reason for delay

7.4.2.2 Infusion Interruptions and Rate Changes

Each nivolumab or ipilimumab infusion can be interrupted and/or the IV infusion rate can be reduced. This information will be retrieved from CRF dosing pages.

- The following parameters will be summarizedby study therapy (nivolumab and ipilimumab) for all treated subjects, and by cohort and SRT status:
- Number of subjects with at least one dose infusion interruption, the reason for interruption, and the number of infusion interruptions per subject.
- Number of subjects with at least one IV infusion rate reduction and the reason for reduction.

7.4.2.3 Dose Escalations

Dose escalations are not permitted for either nivolumab or ipilimumab.

7.4.2.4 Dose Reductions

Dose reductions are not permitted for either nivolumab or ipilimumab.

7.4.2.5 Dose Omissions

Dose omissions are not permitted for either nivolumab or ipilimumab.

7.4.4 *Diagnostic Procedures*

- By-subject listings of Diagnostic procedures will be provided for all treated subjects.

7.5 Efficacy

All summaries will be based on all treated subjects, unless otherwise specified. All summaries will be repeated by cohort and by SRT status, unless otherwise specified.

7.5.1 *Primary Efficacy Analysis*

The primary endpoint of intracranial CBR is determined by modified RECIST 1.1 criteria for index intracranial lesions based on investigator review. The intracranial CBR will be calculated for the all treated population with its corresponding two sided 90% exact CI using the Clopper-Pearson method. The two-sided 95% CI will also be calculated.

CBR based on BOR as reported on CRF will be analyzed using the same methodology as primary endpoint of intracranial CBR based on modified RECIST 1.1.

Central review of all images will be conducted by a Blinded Independent Central Review (BICR) specified in the Imaging Review Charter. In addition to the primary endpoint analysis, a sensitivity analysis using BICR-assessed intracranial CBR will also be performed, where both two-sided 90% exact CI and two-sided 95% CI will be calculated.

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. This will be repeated by cohort only.

7.5.2 *Secondary Efficacy Analyses*

Secondary analyses include additional CBR results, Objective Response Rate (ORR), overall survival (OS) including OS within tumor response and prior occurrence of specific AEs, subject follow-up, subsequent therapy and progression free survival.

7.5.2.1 Clinical Benefit Response Rate

For CBR (extracranial and global) the analyses will use a similar approach as for intracranial CBR described above. Rates will be estimated and the corresponding two-sided 95% CI will be calculated by Clopper-Pearson method.

7.5.2.2 Objective Response Rate

For ORR (intracranial, extracranial and global) the analyses will use a similar approach as for intracranial CBR described above. Rates will be estimated and the corresponding two-sided 95% CI will be calculated by Clopper-Pearson method. BOR (intracranial, extracranial and global) will be tabulated, and listed, including reasons for not evaluable BOR.

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

To assess consistency of effect in ORR in different subsets, "forest" plots of the ORRs and CBRs and corresponding exact 95% CIs using the Clopper and Pearson method will be produced for intracranial, extracranial and global results for the following subgroups:

- PD-L1 Status (<1% vs >=1%, <5% vs >=5%, <10% vs >=10%)
- BRAF mutation status (BRAF mutant and wildtype)
- NRAS mutation status (NRAS mutant and wildtype)
- Age category I (< 65 and ≥ 65)
- Age category II (< 65, ≥ 65- < 75, and ≥ 75)
- Gender (male and female)
- Race (white, black, asian, and other)
- Baseline ECOG Performance Status (0 and 1)
- Baseline LDH (≤ ULN and > ULN)
- Baseline LDH (≤ 2*ULN and > 2*ULN)
- Disease Stage at Study Entry (Stage III, Stage IV)
- SRT Prior to Study Entry (Yes, No)
- Number of Target Lesions (0, 1-2, >=3)
- Each forest plot will include a column for number of subjects, number of responses and ORR/CBR with 95% CI. Within each subgroup, a "NOT REPORTED" category will be added if subject has missing value.
- A cross tabulation of BICR BOR versus the investigator BOR determined by modified RECIST1.1 criteria will be presented overall and by response categories, for intracranial, extracranial and global results. Concordance Rate of Responders will be computed as the frequency with which investigator and BICR agree on the classification of a subject as responder vs. non-responder/Unable to Determine (UTD) as a proportion of the total number of treated subjects assessed by both the investigator and BICR.

7.5.2.3 Overall Survival

Overall survival will be estimated using the Kaplan-Meier product limit method, together with a two-sided 95% confidence interval for the median, calculated using the method of Brookmeyer and Crowley method. Median overall survival (OS) will be estimated using Kaplan-Meier product-limit method.

Survival rates at 6, 9, 12, 18, 24, 36, 48 months will be estimated using KM estimates on the OS curve. Minimum follow-up must be longer than the timepoint to generate the rate. Associated two-sided 95% CIs will be calculated. Results will be tabulated and plotted.

The status of subjects who are censored in the OS KM analysis will be tabulated for the following categories:

- on-study (on-treatment and not progressed, on-treatment progressed, in follow-up)
- off-study: (lost to follow-up, withdrew consent, etc.)

To assess consistency of treatment effect in OS in different subgroups, a 'forest' plot of the OS rate at 6 month and two-sided 95% CIs based on Kaplan-Meier estimates will be produced for the same variables as in section 7.5.2.1.

Overall survival data will also be listed.

7.5.2.4 OS by Tumor Response

Exploratory analyses of survival by response category will be analyzed using the landmark method[14]. Subjects still on study at the landmark time will be separated into two response categories according to whether they have responded before that time. This will assess whether survival from the landmark depends on the subject's response status at the landmark. Subjects who go off protocol (e.g., subjects who die) before the time of landmark will be excluded from the analysis.

The survival curves from Week 12 and Month 6 by intracranial response status will be produced using the KM product-limit method. Two sided, 95% CIs for median OS will be computed.

7.5.2.5 OS by Prior Occurrence of Select AE

Exploratory analyses of survival by prior occurrence of select AE will be analyzed using the landmark method[14]. For each select AE category subjects still on study at the landmark time will be separated into two categories according to whether they have had an occurrence of an AE in the category before that time. This will assess whether survival from the landmark depends on the occurrence of a select AE at the landmark. Subjects who go off protocol (e.g., subjects who die) before the time of landmark will be excluded from the analysis.

The survival curves from Week 9, Month 4, Month 6, Month 8 and Month 12 by prior occurrence status will be produced using the KM product-limit method. Two sided, 95% CIs for median OS will be computed.

7.5.2.6 Subject Follow-Up

The extent of follow-up defined as the time between first dosing date and last known date alive (for subjects who are alive) or death date (for subjects who died) will be summarized descriptively (mean, median, min, max, standard deviation) for all treated subjects.

The currentness of follow-up, defined as the time between last OS contact (i.e., last known date alive or death date) and data cut-off date, will be summarized. Subjects who died before data cut-off date will automatically have zero value for currentness of follow-up. For subjects with last known date alive after data cut-off date, they will have zero value for currentness of follow-up as well. The currentness of follow-up will be categorized into the following categories: 0 days, 1-30 days, 31-60 days, 61-90 days, 91-120 days, 121-150 days, 151 or more days.

Minimum follow-up for OS, defined as difference in time from data cut-off date to last subject's first treatment date, will be summarized in months.

7.5.2.7 Subsequent Therapy

Subsequent therapy will be summarized and listed.

- Subsequent Therapy

  Chemotherapy by drug name

  Hormonal or biologic therapy by drug name

  Immunotherapy (anti-PD1 agents, anti-PDL1 agents, anti-CTLA4 agents, and others) by drug name

  BRAF inhibitor by drug name

  MEK/NRAS inhibitor by drug name

  Other investigational agent by drug name

  Surgery

  Radiotherapy

  Systematic therapy

  Any combination of the above
- By Subject Listing of Subsequent Therapy

7.5.2.8 Progression Free Survival

The intracranial, extracranial and global PFS will be estimated using the Kaplan-Meier product-limit method, together with a two-sided 95% confidence interval for the median, calculated using the method of Brookmeyer and Crowley method.

PFS rates at 6, 12, 18, 24, 36, 48 months, and then every year will be estimated using KM estimates on the PFS curve. Minimum follow-up must be longer than the timepoint to generate the rate. Associated two-sided 95% CIs will be calculated. Results will be tabulated and plotted.

The source of progression event (death versus progression) will be summarized.

The status of subjects who are censored in the PFS KM analysis will be tabulated using the following categories:

- On-study (on-treatment, in follow-up)
- Off-study (lost to follow-up, withdrawn consent, never treated)
- Received subsequent anticancer therapy

All PFS data will be listed. In addition, a listing of subjects who were treated beyond progression will also be presented.

Sensitivity analyses using BICR-assessed PFS (intracranial, extracranial, and global) will also be performed for the above analyses and BICR PFS data will be listed.

In addition, to assess consistency of treatment effect in PFS in different subgroups, a 'forest' plot of the PFS rate at 6 month and two-sided 95% CIs based on Kaplan-Meier estimates will be produced on intracranial, extracranial and global PFS for the same variables as in section 7.5.2.2.

Primary censoring rules for the analysis of PFS are presented in Table 7.5.2.8-1.

Table 7.5.2.8-1: Censoring Scheme for Primary Definition of PFS

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessment	Date of first study treatment	Censored
No on-study tumor assessments and no death	Date of first study treatment	Censored
Documented progression	Date of first documented progression per RECIST 1.1 (excludes clinical progression)	Progressed
No progression and no death	Date of last evaluable tumor assessment	Censored
New anticancer therapy, tumor-directed radiotherapy, or tumor-directed surgery received without progression reported prior or on the same day	Date of last evaluable tumor assessment prior to initiation of subsequent therapy	Censored
Death without progression	Date of death	Progressed

[redacted]

In addition, a categorical summary of DOR will be presented for intracranial, extracranial and

7.5.4 Interim Analyses

To assess safety and tolerability, one interim analysis was conducted for this study after 20 subjects completed induction treatment or discontinued for any reason. Descriptive analyses on both efficacy and safety were conducted on these 20 treated subjects. No statistical test was performed.

7.6 Safety

The evaluation of safety is based on clinical AEs (including SAEs and death), vital signs, ECG results, clinical laboratory results, and concomitant medications, reported during the study. Safety results will be summarized for all treated subjects by cohorts and by SRT status.

7.6.1 Deaths

Deaths will be summarized for all treated subjects and by cohorts and by SRT status:

- All deaths, reasons for death
- Deaths within 30 days of last dose received, reasons for death
- Deaths within 100 days of last dose received, reasons for death

By-subject listing of deaths will be provided for all treated subjects.

7.6.2 Serious Adverse Events

Serious adverse events will be summarized for all treated subjects, and by cohorts and by SRT status:

- Overall summary of SAEs by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by SOC/PT
- Overall summary of SAEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT for events occurring in 1% of treated subjects.
- Overall summary of drug-related SAEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT

All analyses will be conducted using the 30-day safety window and repeated using the 100-day safety window.

By-subject SAE listing will be provided for all enrolled subjects.

7.6.3 Adverse Events Leading to Discontinuation of Study Therapy

AEs leading to discontinuation will be summarized for all treated subjects, and by cohorts and by SRT status:

- Overall summary of AEs leading to discontinuation by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by SOC/PT
- Overall summary of AEs leading to discontinuation by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT
- Overall summary of drug-related AEs leading to discontinuation by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by SOC/PT
- Overall summary of drug-related AEs leading to discontinuation by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT

The analyses will be conducted using the 30-day safety window and repeated using the 100-day safety window.

By-subject AEs leading to discontinuation listing will be provided.

7.6.4 Adverse Events Leading to Dose Modification

AEs leading to dose delay/reduction will be summarized for all treated subjects, and by cohorts and by SRT status:

- Overall summary of AEs leading to dose delay/reduction by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by SOC/PT

The analysis will be conducted using the 30-day safety window and repeated using the 100-day safety window.

By-subject AEs leading to dose delay/reduction listing will be provided.

7.6.5 Adverse Events

AEs will be summarized for all treated subjects and by cohorts and by SRT status. The following analyses will be conducted:

- Overall summary of any AEs by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by SOC/PT
- Overall summary of any non-serious AEs presented by SOC/PT. This table will be restricted to events with an incidence greater or equal to 5% in all treated subjects.
- Overall summary of any AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT. This table will be restricted to events with an incidence greater or equal to 5% in all treated subjects.
- Overall summary of drug-related AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT
- Overall summary of any AEs that required immune modulating medication by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.

The analyses will be conducted using the 30 days as well as 100 days extended safety window.

In addition, overall summary of late-emergent drug-related AEs (defined as drug-related events reported beyond 100 days after last dose of study therapy) by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) will be presented by SOC/PT.

By-subject AE listing and by-subject listing of any AE requiring immune modulating medications will be provided for all treated subjects.

7.6.6 Multiple Events

The following summary tables will be provided for all treated subjects, and by cohorts and by SRT status

- A table showing the total number and rate (exposure adjusted) of occurrences for AEs occurring in at least 5% of treated subjects

- For select AEs, a table showing the number of subjects experiencing an AE once or multiple times

In addition, the rate (exposure adjusted) and its 95% CI evaluated for different time intervals will be displayed graphically. This analysis will be limited to the rate of all AEs and all drug-related AEs.

The analyses will be conducted using the 30 days as well as 100 days extended safety window.

A listing displaying the unique instances of all AEs, i.e., after duplicates have been eliminated and overlapping and contiguous occurrences of the same event (i.e. same PT) have been collapsed will be provided.

7.6.7 Select Adverse Events

Unless otherwise specified, analyses will be performed by select AE category. Some analyses may also be repeated by subcategory of endocrine events (APPENDIX 1).

7.6.7.1 Incidence of Select AE

Select AEs (see Table 11-3) will be summarized for all treated subjects and by cohorts and by SRT status for each category/subcategory:

- Overall summary of any select AEs by worst CTC grade presented by Category or Subcategory/PT (any grade, grade 3-4, grade 5)
- Overall summary of any drug-related select AEs by worst CTC grade presented by Category or Subcategory/PT (any grade, grade 3-4, grade 5)
- Overall summary of any serious select AEs by worst CTC grade presented by Category or Subcategory/PT (any grade, grade 3-4, grade 5)
- Overall summary of drug-related serious select AEs by worst CTC grade presented by Category or Subcategory/PT (any grade, grade 3-4, grade 5)
- Overall summary of any select AEs leading to discontinuation by worst CTC grade presented by Category or Subcategory/PT (any grade, grade 3-4, grade 5)
- Overall summary of any drug-related select AEs leading to discontinuation by worst CTC grade by Category or Subcategory/PT (any grade, grade 3-4, grade 5)

The analyses will be conducted using the 30 days as well as 100 days extended safety window.

By-subject select AE listing will be provided.

7.6.7.2 Time to Onset of Select AE

Time-to-onset of the following specific events will be graphically displayed for each category of select AEs using the Kaplan-Meier technique for all treated subjects and by cohorts and by SRT status:

- Time-to onset of any grade select AE
- Time-to onset of grade 3 to 5 select AE
- Time-to onset of any grade drug-related select AE
- Time-to onset of grade 3 to 5 drug-related select AE

In addition, median time-to-onset along with 95% CI (derived from Kaplan-Meier estimation) and ranges will be tabulated for each of the above analyses and for endocrine subcategories.

Rates (derived from the graph) by landmark timepoints will be tabulated for these specific events and for each treatment group.

Additional details regarding the time-to-onset definition and censoring rules are described in time-to-onset definition subsection of APPENDIX 1.

The analyses will be conducted using the 30 days as well as 100 days extended safety window, except for endocrine subcategories which will be presented for the 30 days window only.

7.6.7.3 Time to resolution of Select AE

Time to resolution of the following specific events will be summarized separately for each category/subcategory for all treated subjects and by cohorts and by SRT status:

- Time-to resolution of any grade select AE
- Time-to resolution of grade 3 to 5 select AE
- Time-to resolution of any grade drug-related select AE
- Time-to resolution of grade 3 to 5 drug-related select AE
- Time-to resolution of any grade select AE where immune modulating medication was initiated
- Time-to resolution of grade 3 to 5 select AE where immune modulating medication was initiated
- Time-to resolution of any grade drug-related select AE where immune modulating medication was initiated
- Time-to resolution of grade 3 to 5 drug-related select AE where immune modulating medication was initiated

Time-to-resolution analyses are restricted to treated subjects who experienced the specific events. Analyses of time-to-resolution where immune modulating medication was initiated are restricted to treated subjects who experienced the specific events and who received immune modulating medication during the longest select AE.

The analyses will be conducted using the 30 days as well as 100 days extended safety window, except for endocrine subcategories which will be presented for the 30 days window only.

The following summary statistics will be reported: percentage of subjects who experienced the specific events, percentage of subjects with resolution of the longest select AE, median time-to-resolution along with 95% CI (derived from Kaplan-Meier estimation) and ranges.

Additional details are described in the time-to-resolution definition subsection of APPENDIX 1.

7.6.8 Other Adverse Events of Special Interest

Time to onset and time to resolution of Nervous system disorders AEs (identified using MedDRA SOC) will be summarized as follows:

Time-to-onset will be tabulated for all treated subjects and by cohorts and by SRT status. Median time-to-onset along with 95% CI (derived from Kaplan-Meier estimation) and ranges will be presented, as per section 7.6.7.2:

- Time-to onset of any grade
- Time-to onset of grade 3 to 5
- Time-to onset of any grade drug-related
- Time-to onset of grade 3 to 5 drug-related

Time to resolution will be summarized for all treated subjects and by cohorts and by SRT status, as per section 7.6.7.3:

- Time-to resolution of any grade
- Time-to resolution of grade 3 to 5
- Time-to resolution of any grade drug-related
- Time-to resolution of grade 3 to 5 drug-related
- Time-to resolution of any grade where immune modulating medication was initiated
- Time-to resolution of grade 3 to 5 where immune modulating medication was initiated
- Time-to resolution of any grade drug-related where immune modulating medication was initiated
- Time-to resolution of grade 3 to 5 drug-related select AE where immune modulating medication was initiated

The analyses will be conducted using the 30 days as well as 100 days extended safety window.
Other adverse events of special interest (AEOSI) consist of a list of preferred terms grouped by specific category (e.g. Myositis Event, Myocarditis Event, Demyelination Event, Guillain-Barre Syndrome, Pancreatitis Event, Uveitis Event, Encephalitis Event, etc.). The list of MedDRA preferred terms used to identify AEOSI is revisited quarterly and updated accordingly. The preferred terms used for the selection at the time of the database lock by categories will be provided.
Other AEs of special interest will be summarized by cohorts and by SRT status for each category.

- The following analyses will be conducted using the 30 days safety window and repeated using 100 days extended safety window:
- Overall summary of other AEs of special interest by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category / PT
- Overall summary of other AEs of special interest by worst CTC grade (grade 1, 2, 3, 4 ,5, unknown) presented by Category / PT
- Overall summary of drug-related other AEs of special interest by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category / PT
- Overall summary of drug-related other AEs of special interest by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by Category / PT
- Summaries of time to onset and time to resolution of other AEs of special interest by worst CTC grade (any grade, grade 3-5) presented by Category

- Summaries of time to onset and time to resolution of drug-related other AEs of special interest by worst CTC grade (any grade, grade 3-5) presented by Category
- Overall summary of serious other AEs of special interest by worst CTC grade presented by Category / PT (grade 1, 2, 3, 4 ,5, unknown)
- Overall summary of other AEs of special interest leading to discontinuation by worst CTC grade presented by Category / PT (grade 1, 2, 3, 4 ,5, unknown)
- All above summaries are done using all treated subjects, except the summaries of time to onset/resolution are on treated subjects who experienced at least one other event of special interest from the category.
- The following analyses will be conducted using the 100-day extended safety window only:
- Overall summary of other AEs of special interest by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category / PT where immune-modulating medication was initiated
- Overall summary of other AEs of special interest by worst CTC grade (grade 1, 2, 3, 4 ,5, unknown) presented by Category / PT where immune-modulating medication was initiated
- Overall summary of drug-related other AEs of special interest by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category / PT where immune-modulating medication was initiated.
- Overall summary of drug-related other AEs of special interest by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by Category / PT where immune-modulating medication was initiated.
- Summaries of time to onset and time to resolution of other AEs of special interest by Category where immune-modulating medication was initiated.
- Overall summary of immune modulating concomitant medication for other AEs of special interest management by worst CTC grade (any grade, grade 3-5) presented by Category / PT

All above summaries are done using all treated subjects, except the summaries mentioned in the last two bullets are on treated subjects who experienced at least one other event of special interest from the category. By-subject listings of other AEs of special interest and other AEs of special interest definition will be provided.

7.6.9 Adverse Events By Subgroup

Overall summary of any AEs and drug-related AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT for all treated subjects and by cohorts and SRT status, for the following subgroups:

- Gender (Male vs. Female)
- Race
- Age (<65 vs. 65-<75 vs. 75-<85 vs. >= 85 vs. >= 75 vs. >= 65)
- Dexamethasone exposure (Yes vs. No) (Cohort B Only)

7.6.10 Immune Modulating Medication

Immune modulating concomitant medications are medications selected from the most current pre-defined list of immune modulating medications.

- The following will be tabulated by medication class and generic term, for all treated subjects and by cohort and SRT status.

The percentage of subjects who received immune modulating concomitant medication for:

- management of adverse event
- premedication
- other use
- any use
- management of drug-related select adverse event (any grade, grade 3-5) by select AE category/ subcategory
- management of IMAEs (any grade, grade 3-5) by IMAE category

For each category/subcategory of select AEs (see Table 11-3), the following will be reported:

- Percentage of subjects who received immune modulating concomitant medication for management of any select AE in the category among subjects who experienced at least one select adverse event in the category/subcategory.
- The total medication treatment duration (summary statistics)

These analyses will be performed on any select AEs, drug-related select AEs, grade 3-5 select AEs, drug-related grade 3-5 select AEs and immune-mediated AEs.

For select AEs, the analyses will be conducted using the 30-day safety window and repeated using the 100-day safety window, except for endocrine subcategories which will be presented for the 30 days window only, and immune mediated AEs which will be presented for the 100 days window only.

7.6.11 Immune-Mediated Adverse Events

In order to further characterize AEs of special clinical interest analysis of immune-mediated AEs (IMAE) will be conducted. Immune-mediated AEs are specific events (or groups of PTs describing specific events) that include pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, endocrine (adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis), and other specific events, considered as potential immune-mediated events by investigator, that meet the definition summarized below:

- those occurring within 100 days of the last dose,
- regardless of causality,
- treated with immune-modulating medication (of note, endocrine Adverse events such as adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis are considered IMAEs regardless of immune-modulating medication use, since endocrine drug reactions are often managed without immune-modulating medication).

The list of MedDRA preferred terms used to identify Immune-Mediated adverse events is revisited quarterly and updated accordingly. The preferred terms used for the selection at the time of the database lock by categories will be provided.

IMAEs will be summarized by treatment group for each immune mediated category / PT using the 100-day safety window:

- Overall summary of AEs by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by immune mediate Category / PT. This summary includes all AEs that are qualified for IMAE preferred terms list, without requirement of either usage of immune modulating medications or accounting for immune mediated etiology or immune mediated component.
- Overall summaries of IMAEs by worst CTC grade [(grade 1, 2, 3, 4, 5, unknown) and (any grade, grade 3-4, grade 5)] where immune modulating medication was initiated presented by Category / PT.
- Overall summaries of endocrine IMAEs by worst CTC grade [(grade 1, 2, 3, 4, 5, unknown) and (any grade, grade 3-4, grade 5)] presented by Category / PT.
- Overall summaries of serious IMAEs by worst CTC grade [(grade 1, 2, 3, 4, 5, unknown) and (any grade, grade 3-4, grade 5)] where immune modulating medication was initiated presented by Category / PT.
- Overall summaries of endocrine serious IMAEs by worst CTC grade [(grade 1, 2, 3, 4, 5, unknown) and (any grade, grade 3-4, grade 5)] presented by Category / PT.
- Overall summaries of IMAEs leading to discontinuation by worst CTC grade [(grade 1, 2, 3, 4, 5, unknown) and (any grade, grade 3-4, grade 5)] where immune modulating medication was initiated presented by Category / PT.
- Overall summaries of endocrine IMAEs leading to discontinuation by worst CTC grade [(grade 1, 2, 3, 4, 5, unknown) and (any grade, grade 3-4, grade 5)] presented by Category / PT.
- Overall summaries of IMAEs leading to dose delay or reduction by worst CTC grade [(grade 1, 2, 3, 4, 5, unknown) and (any grade, grade 3-4, grade 5)] where immune modulating medication was initiated presented by Category / PT
- Overall summaries of endocrine IMAEs leading to dose delay or reduction by worst CTC grade [(grade 1, 2, 3, 4, 5, unknown) and (any grade, grade 3-4, grade 5)] presented by Category / PT.
- Summaries of time to onset and time to resolution of IMAEs where immune modulating medication was initiated presented by Category.
- Summaries of time to onset and time to resolution of endocrine IMAEs presented by Category.

By-subject listing of IMAEs and listing of IMAE definition will be provided. By-subject listings of time to resolution for longest IMAEs cluster (any grade and grade 3-5 in separate summaries) will also be provided.

In addition, for all nivolumab treated subjects who experienced at least one immune-mediated adverse event, the following data presentation will be provided:

- Summary of subjects who were re-challenged with nivolumab by immune-mediated adverse event category, with extended follow-up

- Summary of subjects who were re-challenged with nivolumab or ipilimumab by immune-mediated adverse event category with extended follow-up

For these, re-challenge is considered to have occurred when last nivolumab and/or ipilimumab infusion was administered after the onset of an IMAE.

7.6.12 Clinical laboratory evaluations

7.6.12.1 Hematology

The following will be summarized for all treated subjects, and by cohorts and by SRT status, as worst CTC grade on-treatment per subject and as shift table of worst on-treatment CTC grade compared to baseline CTC grade per subject: hemoglobin, platelets, white blood counts, absolute neutrophils count and lymphocyte count.

The analyses will be conducted using the 30-day safety window and repeated using the 100-day safety window.

A by-subject listing of these laboratory parameters will be provided.

7.6.12.2 Serum Chemistry

The following will be summarized for all treated subjects, and by cohorts and by SRT status, as worst CTC grade on-treatment per subject and as shift table of worst on-treatment CTC grade compared to baseline CTC grade per subject: ALT, AST, alkaline phosphatase, total bilirubin, creatinine, amylase and lipase.

The analyses will be conducted using the 30-day safety window and repeated using the 100-day safety window.

A by-subject listing of these laboratory parameters will be provided.

7.6.12.3 Electrolytes

The following will be summarized by treatment group as worst CTC grade on-treatment per subject and as shift table of worst on-treatment CTC grade compared to baseline CTC grade per subject: sodium (high and low), potassium (high and low), calcium (high and low), magnesium (high and low).

The analyses will be conducted using the 30-day safety window and repeated using the 100-day safety window.

A by-subject listing of these laboratory parameters will be provided.

7.6.12.4 Additional Analyses

In addition, the following analyses on specific laboratory parameters will be performed for all treated subjects, by cohorts and SRT status:

<u>Abnormal Hepatic Function Test</u>

The number of subjects with the following laboratory abnormalities from on-treatment evaluations will be summarized:

- ALT or AST > 3 x upper limit of normal (ULN), > 5 x ULN, > 10 x ULN and > 20 x ULN
- Total bilirubin > 2 x ULN
- Concurrent (within 1 day) ALT or AST > 3 x ULN and total bilirubin > 2 x ULN
- Concurrent (within 30 days) ALT or AST > 3 x ULN and total bilirubin > 2 x ULN

The following scatterplots will be produced for the following hepatic laboratory parameters:

- Total bilirubin peak vs. AST peak
- Total bilirubin peak vs. ALT peak

On-treatment peak total bilirubin and on-treatment peak AST/ALT may or may not happen on the same day of liver testing.

- The analyses will be conducted using the 30-day safety window and repeated using the 100-day safety window.
- A by-subject listing of these specific abnormalities will be provided.

Abnormal Thyroid Function Test

The number of subjects with the following laboratory abnormalities from on-treatment evaluations will be summarized for all treated subjects, and by cohorts and by SRT status:

- TSH value > ULN and
  with baseline TSH value ≤ ULN
  at least one FT3/FT4 test value < LLN
  with all other FT3/FT3 test values >=LLN
  with FT3/FT4 test missing
- TSH < LLN and
  - with baseline TSH value ≥ LLN
    at least one FT3/FT4 test value > ULN
    with all other FT3/FT3 test values <=LLN
    with FT3/FT4 test missing

The analyses will be conducted using the 30-day safety window and repeated using the 100-day safety window.

A by-subject listing of these specific abnormalities will be provided.

7.6.13 Vital Signs

Vital signs consist of blood pressure, heart rate, respiratory rate and temperature measurements will be summarized and listed for all treated subjects. Summaries of vital signs will be provided for each parameter. The actual values by visit, and changes from baseline for post-baseline visits will be summarized by cohorts and by SRT status.

A summary table on weight reduction (Reduction>=5%, None) based on last measurement will also be presented by cohorts and by SRT status.

A by-subject listing of all vital signs will be provided. Subjects with vital signs out of pre-specified range will also be listed.

The following criteria will be used to determine vital sign results that are outside of a pre-specified range, where changes from baseline are based on matched postural positions and are calculated as parameter value - baseline parameter value:

Table 3: Out-of-Range Vital Sign Criteria

Heart Rate(bpm)	Value > 100 and change from baseline > 30, or Value < 55 and change from baseline < -15
Systolic BP(mmHg)	Value > 140 and change from baseline > 20, or Value < 90 and change from baseline < -20
Diastolic BP(mmHg)	Value > 90 and change from baseline > 10, or Value < 55 and change from baseline < -10
Respiration(breaths/min)	Value > 16 or change from baseline > 10
Temperature (°C)	Value > 38.3°C or change from baseline > 1.6°C

7.6.14 Electrocardiogram

By-subject listing of ECG test results will be provided for all treated subjects.

7.6.15 Physical Examination Findings

All abnormal physical examination findings will be listed per subject and visit for all treated subjects.

7.6.16 Pregnancy

By-subject listing of pregnancy tests results will be provided for all treated female subjects.

[redacted]

expression as a predictive biomarker, including selection of an optimal PD-L1 expression cut-off

[redacted]

8 CONVENTIONS

All statistical analyses will be carried out using SAS (Statistical Analysis System software, SAS Institute, North Carolina, USA) unless otherwise noted.

Safety conventions from Programming are summarized in the core safety SAP.

8.1.1 Decimal Places

The number of decimal places displayed in all listings will be determined by the number of decimal places in the raw data.

Unless otherwise specified, minimum and maximum will be reported to the precision as the data collected, one more decimal place for the mean and median, and two more decimal places for the standard deviation. The adjusted geometric mean, geometric mean ratio and the lower and upper limits of confidence interval will be displayed to three decimal places.

8.1.2 Partial Date Imputation

The following conventions may be used for imputing partial dates for analyses requiring dates:

For missing and partial AE onset dates, imputation will be performed using the Adverse Event Domain Requirements Specification. Missing and partial Non-Study Medication Domain dates will be imputed using the derivation algorithm described in BMS Non-Study Medication Domain Requirements Specification.

For death dates, the following conventions will be used for imputing partial dates:

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day. The imputed date will be compared to the last known date alive +1 day and the maximum will be considered as the death date.
- If the month or the year is missing, the death date will be imputed as the last known date alive + 1 day
- If the date is completely missing but the reason for death is present the death date will be imputed as the last known date alive + 1 day
- For date of progression, the following conventions will be used for imputing partial dates:
- If only the day of the month is missing, the 1st of the month will be used to replace the missing day*.
- If the day and month are missing or a date is completely missing, it will be considered as missing.
- * In case, the date of death is present and complete, the imputed progression date will be compared to the date of death. The minimum of the imputed progression date and date of death will be considered as the date of progression.
- For other partial/missing dates, the following conventions will be used:
- If only the day of the month is missing, the 15th of the month will be used to replace the missing day.
- If both the day and the month are missing, "July 1" will be used to replace the missing information.
- If a date is completely missing, it will be considered as missing.

The following conversion factors will be used to convert days to months or years: 1 month = 30.4375 days and 1 year = 365.25 days.

Duration (e.g. time from first diagnosis of Non-small Cell Lung Cancer (NSCLC) to first dosing date, duration response, and time to response) will be calculated as follows:

Duration = (Last date - first date + 1)

Last known date alive will be defined based on all appropriate dates collected on the CRF.

9 CONTENT OF REPORTS

The complete list of analyses contributing to the clinical study report is given in the Data Presentation Plan.

[redacted]

APPENDIX 1 SELECT ADVERSE EVENTS DEFINITION AND CONVENTIONS

The select AEs consist of a list of PT grouped by specific category (e.g. pulmonary events, gastrointestinal events categories) and by subcategory (e.g. thyroid disorders, diabetes, pituitary, adrenal disorders subcategories). These categories and subcategories are defined by the Sponsor and the list that is most current at the time of analysis will be used. Also changes may be made to this list with each new version of MedDRA.

For information, the select AEs defined at the time of finalization of the first version of the document are listed in Table 11-3 using MedDRA version 16. The final list used for the clinical study report will be included in an Appendix of the CSR.

Time-to onset definition

Time-to onset of select AE (any grade) for a specific category (i.e. pulmonary events, gastrointestinal events, ...) is defined as the time between the day of the first dose of study treatment and the onset date of the earliest select AE (of any grade) in this category.

If the subject did not experience a select AE (of any grade) in the category, time-to onset will be censored at the maximum follow-up time of all subjects in their respective treatment group (i.e. for subjects without an event, follow-up time is defined from first dosing date up to last dosing date +30 days (or 100 days depending on the analysis) if subjects are off treatment and followed for at least 30 days (or 100 days depending on the analysis) , otherwise it is defined up to the last known alive date). The resulting Kaplan-Meier plot will represent the cumulative rate of the select AE (any grade) in the category over time.

Time-to onset of select AE (grade 3-5) for a specific category is defined similarly but restricted to grade 3-5 select AEs.

Time-to onset of drug-related (grade 3-5 or any grade) select AE for a specific category is defined similarly but restricted to drug-related select AEs.

Time-to onset for a specific subcategory is defined similarly but restricted to event of this subcategory.

Time-to resolution definition

In order to derive the time-to resolution, overlapping or contiguous select AEs within a specific category (defined in Table 11-3) will be collapsed into what will be termed "clustered" select AEs. For example, if a subject (without pre-treatment AE) experienced an AE from 1st to 5th January, another AE (with different PT but within same category) from 6th to 11th January and same AE from 10th to 12th January, these will be collapsed into one clustered select AE from 1st to 12th January. Table 11-2 is summarizing key derivation steps for each type of clustered select AEs.

Time-to resolution of select AE (any grade) for a specific category is defined as the longest time from onset to complete resolution or improvement to the grade at baseline among all clustered select AEs in this category experienced by the subject. Events which worsened into grade 5 events (death) or have a resolution date equal to the date of death are considered unresolved. If a clustered

select AE is considered as unresolved, the resolution date will be censored to the last known date alive. Improvement to the grade at baseline implies that all different AE events in the clustered select AE should at least have improved to the corresponding (i.e. with same PT) baseline grade. This measure is defined only for subjects who experienced at least one select AE in the specific category.

The time-to resolution of select AE (grade 3-5) for a specific category is defined similarly with an onset date corresponding to a grade 3-5 select AE.

Time-to resolution of drug-related select AE (any grade or grade 3-5) is defined similarly but restricted to drug-related select AE.

The time-to resolution of select AE (any grade or grade 3-5, drug-related or all) where immune modulating medication was initiated is defined similarly with the additional condition that the subject started an immune modulating medication during the longest select AE resolution period.

Time-to resolution for a specific subcategory is defined similarly but restricted to event of this subcategory.

Table 11-2: Derivation of clustered select AE

Type of clustered select AE	Derivation
Any grade	Collapse any on-treatment select AE from the same category
Drug-related of any grade	Collapse any on-treatment drug-related select AE from the same category
Grade 3-5	Collapse any on-treatment select AE from the same category. Resolution will be based on the onset date of the earliest grade 3-5 records (if no grade 3-5 record, clustered select AE is excluded)
Drug-related of Grade 3-5	Collapse any on-treatment drug-related select AE from the same category Resolution will be based on the onset date of the earliest grade 3-5 record (if no Grade 3-5 record, clustered select AE is excluded)

The algorithm for collapsing select AE records is using the following conventions:

For each subject and specified category, the corresponding AE records will be collapsed when:

1) Multiple AE records have the same onset date.
2) The onset date of an event record is either the same day or 1 day later than the resolution date of a preceding event record (contiguous events).
3) The onset date of an event record is after the onset date and prior to or on the resolution date of a preceding event record (overlapping events).

Table 11-3: Select Adverse Events

Category	Subcategory	Preferred Terms
Endocrine Adverse Events	ADRENAL DISORDER	ADRENAL
		ADRENAL SUPPRESSION
		ADRENAL INSUFFICIENCY ACUTE
		BLOOD CORTICOTROPHIN DECREASED
		BLOOD CORTICOTROPHIN INCREASED
		HYPOTHALAMIC PITUITARY ADRENAL AXIS SUPPRESSION
		PRIMARY ADRENAL INSUFFICIENCY
		SECONDARY ADRENOCORTICAL INSUFFICIENCY
	DIABETES	DIABETES MELLITUS
		DIABETIC KETOACIDOSIS
		DIABETIC KETOSIS
		FULMINANT TYPE 1 DIABETES MELLITUS
		LATENT AUTOIMMUNE DIABETES IN ADULTS
		TYPE 1 DIABETES MELLITUS
	PITUITARY DISORDER	HYPOGONADISM
		HYPOPHYSITIS
		HYPOPITUITARISM
		LYMPHOCYTIC HYPOPHYSITIS
	THYROID DISORDER	ATROPHIC THYROIDITIS
		AUTOIMMUNE HYPOTHYROIDISM
		AUTOIMMUNE THYROID DISORDER
		AUTOIMMUNE THYROIDITIS
		BASEDOW'S DISEASE
		BLOOD THYROID STIMULATING HORMONE DECREASED
		BLOOD THYROID STIMULATING HORMONE INCREASED
		HYPERTHYROIDISM
		HYPOPARATHYROIDISM
		HYPOTHYROIDISM
		IMMUNE-MEDIATED HYPERTHYROIDISM
		IMMUNE-MEDIATED HYPOTHYROIDISM
		IMMUNE-MEDIATED THYROIDITIS
		PRIMARY HYPERTHYROIDISM
		PRIMARY HYPOTHYROIDISM
		SILENT THYROIDITIS
		THYROID FUNCTION TEST ABNORMAL
		THYROID HORMONES DECREASED
		THYROID HORMONES INCREASED
		THYROIDITIS
		THYROIDITIS ACUTE
		THYROXINE DECREASED

Table 11-3: Select Adverse Events

Category	Subcategory	Preferred Terms
		THYROXINE FREE DECREASED
		THYROXINE FREE INCREASED
		THYROXINE INCREASED
		TRI-IODOTHYRONINE UPTAKE INCREASED
Hypersensitivity/Infusion Reactions		ANAPHYLACTIC REACTION
		ANAPHYLACTIC SHOCK
		BRONCHOSPASM
		HYPERSENSITIVITY
		INFUSION RELATED HYPERSENSITIVITY REACTION
		INFUSION RELATED REACTION
Gastrointestinal Adverse Events		COLITIS
		DIARRHOEA
		ENTERITIS
		ENTEROCOLITIS
		FREQUENT BOWEL MOVEMENTS
		GASTROINTESTINAL PERFORATION
Hepatic Adverse Events		ACUTE HEPATIC FAILURE
		ACUTE ON CHRONIC LIVER FAILURE
		ALANINE AMINOTRANSFERASE INCREASED
		ASPARTATE AMINOTRANSFERASE INCREASED
		AUTOIMMUNE CHOLANGITIS
		AUTOIMMUNE HEPATITIS
		BILIARY CIRRHOSIS
		BILIRUBIN CONJUGATED DECREASED
		BILIRUBIN CONJUGATED INCREASED
		BLOOD ALKALINE PHOSPHATASE INCREASED
		BLOOD BILIRUBIN INCREASED
		CHOLANGITIS
		DRUG-INDUCED LIVER INJURY
		GAMMA-GLUTAMYLTRANSFERASE INCREASED
		HEPATIC ENZYME INCREASED
		HEPATIC FAILURE
		HEPATITIS
		HEPATITIS ACUTE
		HEPATOTOXICITY
		HYPERBILIRUBINAEMIA
		IMMUNE-MEDIATED CHOLANGITIS

Table 11-3: Select Adverse Events

Category	Subcategory	Preferred Terms
		IMMUNE-MEDIATED HEPATIC DISORDER
		IMMUNE -MEDIATED HEPATITIS
		LIVER DISORDER
		LIVER FUNCTION TEST ABNORMAL
		LIVER FUNCTION TEST INCREASED
		LIVER INJURY
		TRANSAMINASES INCREASED
Pulmonary Adverse Events		ACUTE RESPIRATORY DISTRESS SYNDROME
		ACUTE RESPIRATORY FAILURE
		AUTOIMMUNE LUNG DISEASE
		HYPERSENSITIVITY PNEUMONITIS
		IDIOPATHIC INTERSTITIAL PNEUMONIA
		IMMUNE-MEDIATED PNEUMONITIS
		INTERSTITIAL LUNG DISEASE
		LUNG INFILTRATION
		PNEUMONITIS
Renal Adverse Events		ACUTE KIDNEY INJURY
		AUTOIMMUNE NEPHRITIS
		BLOOD CREATININE INCREASED
		CREATININE RENAL CLEARANCE DECREASED
		END STAGE RENAL DISEASE
		GLOMERULONEPHRITIS RAPIDLY PROGRESSIVE
		HYPERCREATININAEMIA
		NEPHRITIS
		NEPHRITIS ALLERGIC
		PARANEOPLASTIC GLOMERULONEPHRITIS
		RENAL FAILURE
		RENAL FAILURE ACUTE
		RENAL TUBULAR NECROSIS
		TUBULOINTERSTITIAL NEPHRITIS
		URINE OUTPUT DECREASED
Skin Adverse Events		ANAL ECZEMA
		AUTOIMMUNE BLISTERING DISEASE
		AUTOIMMUNE DERMATITIS
		BLISTER

Table 11-3: Select Adverse Events

Category	Subcategory	Preferred Terms
		BULLOUS HAEMORRHAGIC DERMATOSIS
		DERMATITIS
		DERMATITIS ACNEIFORM
		DERMATITIS ALLERGIC
		DERMATITIS ATOPIC
		DERMATITIS EXFOLIATIVE
		DRUG ERUPTION
		ECZEMA
		ENANTHEMA
		ERYTHEMA
		ERYTHEMA MULTIFORME
		ERYTHRODERMIC ATOPIC DERMATITIS
		EXFOLIATIVE RASH
		FIXED ERUPTION
		GUTTATE PSORIASIS
		IMMUNE-MEDIATED DERMATITIS
		MUCOCUTANEOUS DISORDER
		MUCOSA VESICLE
		NODULAR RASH
		PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME
		PARADOXICAL PSORIASIS
		PEMPHIGOID
		PEMPHIGUS
		PHOTOSENSITIVITY REACTION
		PRURITUS
		PRURITUS ALLERGIC
		PSORIASIS
		PUSTULAR PSORIASIS
		PUSTULE
		RASH
		RASH ERYTHEMATOUS
		RASH MACULAR
		RASH MACULO-PAPULAR

Table 11-3: Select Adverse Events

Category	Subcategory	Preferred Terms
		RASH MORBILLIFORM
		RASH PAPULAR
		RASH PRURITIC
		RASH PUSTULAR
		RASH VESICULAR
		SJS-TEN OVERLAP
		SCROTAL DERMATITIS
		SKIN EXFOLIATION
		SKIN IRRITATION
		STEVENS-JOHNSON SYNDROME
		TOXIC EPIDERMAL NECROLYSIS
		TOXIC SKIN ERUPTION
		URTICARIA
		URTICARIAL DERMATITIS
		VITILIGO
		VULVAL ECZEMA