Official Title of Study:

AN OPEN-LABEL, RANDOMIZED, PHASE 2 STUDY OF NIVOLUMAB GIVEN SEQUENTIALLY WITH IPILIMUMAB IN SUBJECTS WITH ADVANCED OR METASTATIC MELANOMA

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STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

AN OPEN-LABEL, RANDOMIZED, PHASE 2 STUDY OF NIVOLUMAB GIVEN SEQUENTIALLY WITH IPILIMUMAB IN SUBJECTS WITH ADVANCED OR METASTATIC MELANOMA

PROTOCOL(S) CA209064

VERSION # 2.0

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

[redacted]

Schedule of Analyses:

The rate of treatment-related Grade 3-5 AEs during the Induction Period (Periods 1 and 2) in subjects receiving sequential induction treatment with either nivolumab followed by ipilimumab (Cohort A) or ipilimumab followed by nivolumab (Cohort B) is the primary endpoint for this study. The final analysis of the primary endpoint will be performed when all randomized subjects have completed/discontinued the Induction Period and all treated subjects with an objective response at Week 25 have been followed through study Week 33 in order to confirm disease response. These conditions are expected to be met at approximately 20 months from the date of first subject first treatment. All secondary endpoints will be analyzed at the time of the primary endpoint analysis.

[redacted]

Additional interim analyses may be performed to support submission and publication needs. In particular, an interim database lock and release of randomized treatment codes will be performed to support a drug manufacturing process biocomparability assessment for nivolumab.

2 STUDY DESCRIPTION

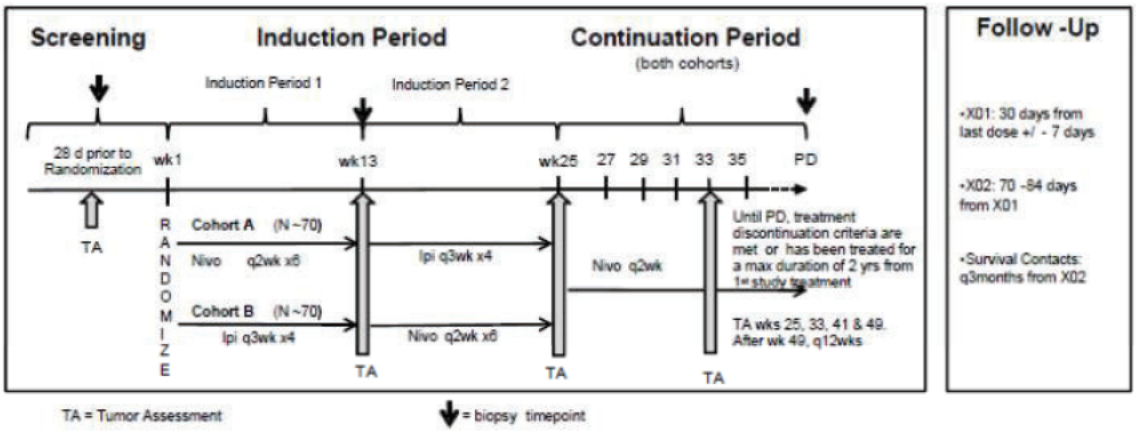
2.1 Study Design

This is an open-label, randomized Phase 2 study of two schedules of nivolumab given sequentially with ipilimumab, in adult (≥ 18 years old) male and female subjects with advanced (unresectable Stage III) or metastatic (Stage IV) melanoma. Approximately 140 subjects will be randomized (1:1) to receive one of two dosing schedules (Cohort A or B).

Assuming a 15% attrition rate of subjects discontinuing study drug before dosing in Induction Period 2, 120 subjects are expected to be treated with at least one dose of study medication (60 per cohort) in both Induction Period 1 and Induction Period 2.

Subjects may be treatment-naive or have experienced disease recurrence or progression after one prior systemic therapy (prior immunotherapy with anti-PD1 or anti CTLA 4 is prohibited). The two dosing schedules to be explored are presented in Figure 2.1-1

Figure 2.1-1: Study Design Schematic



2.2 Treatment Assignment

The subject number will be assigned through an interactive voice response system (IVRS) once the subject has signed the informed consent form and is registered. Every subject that signs the informed consent form must be assigned a subject number in IVRS.

The investigator or designee will register the subject for enrollment by following the enrollment procedures established by BMS. The following information is required for enrollment:

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

Once enrolled in IVRS, enrolled subjects that have signed the informed consent form and met all eligibility criteria will be randomized through the IVRS. The following information is required for subject randomization:

- Subject number
- Date of birth
- Gender at birth
- Date of informed consent

Subjects meeting all eligibility criteria will be randomized in a 1:1 ratio to Cohort A (nivolumab followed by ipilimumab) or Cohort B (ipilimumab followed by nivolumab). Randomization procedures will be carried out via permuted blocks.

2.3 Blinding and Unblinding

Not applicable. This is an open-label study.

2.4 Protocol Amendments

This statistical analysis plan (SAP) incorporates the following amendments:

Table 2.4-1: Protocol Amendments

Amendment	Date of Issue	Summary of Major Changes
Revised Protocol 04 (Incorporates Amendment 08)	12-Mar-2014	The most significant change in this amendment impacts the number of enrolled and randomized patients in the study, increasing both. This was done in order to account for a higher than expected attrition rate prior to treatment in Induction Period 2 [redacted] The current sample size is chosen to achieve a sufficient level of precision for estimating adverse event rates, while simultaneously providing for adequate samples of tumor tissue and peripheral immune cells [redacted] As result of this change, there have been changes to the statistical considerations within the study. Other changes include an update to the dosing interruption clause, removal of the "+3" day portion of the visit window within the Continuation Period, changes to the pregnancy discontinuation wording, and clarifications to the inclusion/exclusion wording. In these cases, the changes were incorporated in order to ensure adequate sample collection, add flexibility, and clarify wording. Additionally, statistical considerations were updated to make the analysis population consistent between primary and secondary endpoints and to allow for potential interim analyses to support submission and publication needs.
Amendment 07 (site specific)	28-Aug-2013	Added a sub-study mandating the collection of peripheral immune cells by leukapheresis and collection of tumor tissue for tumor infiltrating

Table 2.4-1: Protocol Amendments

Amendment	Date of Issue	Summary of Major Changes
		lymphocytes (TILs) (when sufficient tumor tissue is available and suitable for TILs collection) from subjects enrolled at four investigational sites where Amendments 2 and 3 were currently being conducted. All subjects enrolled at the following sites needed to provide written informed consent to undergo these procedures for the purpose of the collection of these samples: [redacted] Amendment 7 replaced Amendments 2 and 3, making the collection mandatory instead of voluntary for all subjects at the designated sites.
Revised Protocol 03 (Incorporates Amendment 06)	14-Aug-2013	In response to an FDA request, added the Women of Childbearing Potential definition to the Inclusion Criteria and to Appendix 2, Guidance on Contraception, of the CA209064 protocol. [redacted]
Revised Protocol 02 (Incorporates Amendment 05)	20-May-2013	Added clarification that a modified version of RECIST 1.1 is being used in this study and provide details on how response is calculated using these criteria. Added opportunistic infection safety information. Updated exclusion criteria to clarify that skin disorders that do not require systemic therapy are not excluded from the study Updated BRAF criteria to exclude subjects who have received prior therapy with a BRAF inhibitor within 6 weeks of enrollment into the study.

Table 2.4-1: Protocol Amendments

Amendment	Date of Issue	Summary of Major Changes
		clarified the window for tumor assessment visits, updating visit windows for tumor assessments and follow-up visits
Revised Protocol 01 (Incorporates Amendment 04)	28-Mar-2013 (Issued prior to first subject, first visit)	Inclusion of pre-clinical safety findings related to reproductive toxicology data. Added Guidance on Contraception Appendix.

3 OBJECTIVES

3.1 Primary

To evaluate the incidence of treatment-related Grade 3-5 AEs during the Induction Period in subjects receiving sequential induction treatment with either nivolumab followed by ipilimumab or ipiliumuab followed by nivolumab

3.2 Secondary

- To evaluate the response rate at Week 25 in subjects receiving sequential induction treatment with either nivolumab followed by ipilimumab or ipilimumab followed by nivolumab
- To evaluate progression rates at Week 13 and Week 25 in subjects receiving sequential induction treatment with either nivolumab followed by ipilimumab or ipilimumab followed by nivolumab

[redacted]

[redacted]

4 ENDPOINTS

4.1 Primary Endpoint: Rate of Treatment-related Grade 3-5 AEs

The primary endpoint of the study is the rate of treatment-related Grade 3-5 AEs during the Induction Period (Periods 1 and 2) in subjects receiving sequential induction treatment with either nivolumab followed by ipilimumab or ipilimumab followed by nivolumab.

The treatment-related Grade 3 - 5 AEs rate is defined as number of subjects who experienced at least 1 treatment related Grade3 - 5 adverse event per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0 criteria, any preferred term with an onset date after or on first day of the Induction Period and not later than discontinuation date from the Induction Period, divided by number of treated subjects. AEs with an onset date after start of subsequent anti-cancer therapy, or start date of Continuation Period treatment will not be included.

- For subjects who discontinue Induction Period early and enter the Follow-Up Period, AEs with onset after the start of the Follow-Up Phase will not be included in the primary endpoint, where first day of Follow-Up Phase is defined as the date the decision was made to discontinue treatment as recorded on the off treatment case report form.
- For subjects who discontinue treatment before the end of Induction Period 1 or 2 but who are eligible to enter the next study period, AEs that occur before end of Induction Period 2 will be included in the primary endpoint, even if they occur after dosing ends while they are waiting to enter the next study period.

By applying the above rules, AEs leading to discontinuation due to toxicity will be counted in the primary endpoint, even if they occur after dosing ends. Conventions for defining the Induction Period for purposes of analysis are described in detail in Section 6.1.

4.2 Secondary Endpoints

4.2.1 Response Rate at Week 25

Response rate at Week 25 is defined as the number of subjects who have a complete response (CR) or partial response (PR) at Week 25 per modified RECIST 1.1 criteria, with confirmation on the scheduled scan at Week 33 (or any subsequent scan performed at least 4 weeks after the Week 25 scan), divided by the total number of treated subjects. Note that the results of the tumor assessment at Week 13 or any unscheduled tumor assessment obtained prior to Week 25, except for baseline/screening tumor assessment, will not be considered in the assessment of response rate at Week 25. This means, for example, that subjects with progressive disease at Week 13 are not precluded from having an assessment of CR or PR at Week 25 for this endpoint if the scan at Week 25 demonstrates such a response.

Conventions for defining the Week 25 study day interval for purposes of analysis are described in Section 8.1. Any treated subject without an evaluable Week 25 time point response (per modified RECIST 1.1) will be considered a non-responder for purposes of the primary analysis

of Week 25 response rate. Such non-evaluable subjects would include those without a baseline tumor assessment and those with no tumor assessment falling within the Week 25 study day analysis window (e.g. due to early discontinuation of induction treatment or improper timing of scheduled tumor assessments).

Evaluations occurring after the date of subsequent anticancer therapy will not be included when determining or confirming response at Week 25. For purposes of the main analysis of this secondary endpoint, anti-cancer therapy will include all interventions listed in Section 7.5.3.2.

4.2.2 Further Characterization of Response Rate at Week 25

Duration of response (DOR) from Week 25 will also be assessed for subjects with confirmed response at Week 25 (see definition above). DOR is defined as the time between the Week 25 date of response and the date of objectively documented disease progression as defined by modified RECIST 1.1 criteria or death, whichever occurs first.

4.2.3 Progression Rates at Weeks 13 and 25

Progression rate at a specific time point is defined as the number of subjects who have Progressive Disease (PD) per modified RECIST 1.1 at that specific time point divided by the total number of treated subjects.

Conventions for defining the Week 13 and Week 25 study day interval for purposes of analysis are described in Section 8.1. As specified by modified RECIST 1.1, the evaluation of PD at Week 13 and Week 25 will use the baseline tumor assessment as reference. For purposes of the primary analysis of progression rates, if a treated subject is missing their tumor assessment at the specified study week, then the results of the previous tumor response evaluation will be carried forward. Both clinical and radiological progressions will be counted as a progression outcome. Subjects who die without a reported prior progression will be considered to have progressed on the date of their death.

[redacted]

[redacted]

5 SAMPLE SIZE AND POWER

This trial is an estimation trial. Sample size in this study is not based on power considerations and will be approximately 140 randomized subjects (70 per cohort). This sample size was chosen to achieve a sufficient level of precision for estimating adverse event rates, while simultaneously providing for adequate samples of tumor tissue and peripheral immune cells to achieve stable estimates for exploratory biomarker analyses.

A projection from ongoing monitoring of this trial indicates the number of subjects randomized but never treated to be approximately 3%. Based on this estimate, it is expected that approximately 136 subjects (68 per cohort) will be treated with at least one dose of study medication. These 'all treated' subjects will be the population used for the primary analysis of the primary endpoint.

Furthermore, it is projected that the number of subjects discontinuing the study prior to treatment in Induction Period 2 will be approximately 15%. Based on this estimate, approximately 120 subjects (60 per cohort) are expected to receive treatment in both Induction Period 1 and Induction Period 2. This subset of subjects who received at least one dose of study treatment in Induction Period 2 will be used in a sensitivity analysis of the primary endpoint.

Tables below provide the 95% confidence intervals computed from different observed rates. Table 5-1 and Table 5-2 indicate what would be the reliability of the AE rate estimates for the primary analysis (N=68 per cohort) and the sensitivity analysis (N=60 per cohort), respectively .

A threshold of 45% will be applied to the upper limit of the confidence interval as an informal guideline for high toxicity

Table 5-1: Exact 95% CI width and upper bound for AE rates up to 40% when observed in 68 subjects

Nb Subj with Rel Gr3-5 A	Rate of Rel Gr3-5 AE	Exact 95% CI width	Upper limit Exact 95%CI
7	10%	16%	20.1%
12	18%	19%	28.8%
15	22%	21%	33.8%
17	25%	22%	37.0%
20	29%	23%	41.7%
22	32%	23%	44.8%
23	34%	24%	46.3%
24	35%	24%	47.8%
27	40%	24%	52.3%

Table 5-2: Exact 95% CI width and upper bound for AE rates up to 40% when observed in 60 subjects.

Nb Subj with Rel Gr3-5 AE	Rate of Rel Gr3-5 AE	Exact 95% CI Width	Upper Limit Exact 95%CI
6	10%	17%	20.5%
12	20%	22%	32.3%
15	25%	23%	37.9%
17	28%	24%	41.4%
18	30%	24%	43.2%
19	32%	25%	45.0%
20	33%	25%	46.7%
24	40%	26%	53.5%

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 evaluations or events that occur 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:

- 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
- Baseline evaluations (tumor response evaluations, laboratory tests, pulse oximetry and vital signs) will be defined as evaluations with a date on or prior to the day of first dose of study treatment

If there are multiple valid assessments, the assessment that is closest to 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.

6.1.2 Post Baseline Period

On-treatment AEs will be defined as AEs with an onset date-time on or after the date-time of the first dose of study treatment (or with an onset date on or after the day of first dose of study treatment if time is not collected or is missing). An AE will be counted as on-treatment if the event occurred within 30 days (or 100 days depending on analysis) of the last dose of study treatment.

On-treatment evaluations (laboratory tests, pulse oximetry 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. An evaluation will be counted as on-treatment if it occurred within 30 days (or 100 days depending on analysis) of the last dose of study treatment.

The Post Baseline Period may be further divided into the following sub-periods. In the definitions below, anti-cancer therapy will include all interventions listed in Section 7.5.3.2, except where otherwise noted.

6.1.2.1 Induction Period 1

AEs during Induction Period 1 will be defined as those with an onset date time on or after the date-time of the first dose of study treatment in Induction Period 1 (or with an onset date on or after the day of first dose of study treatment in Induction Period 1 if time is not collected or is missing) and not later than discontinuation date from the Induction Period 1.

- For subjects who discontinue Induction Period 1 early and enter the Follow-Up Period, AEs with onset after the start of the Follow-Up Phase will not be included, where first day of

Follow-Up Phase is defined as the date the decision was made to discontinue treatment as recorded on the off treatment case report form.

- For subjects who discontinue treatment before the end of Induction Period 1 but who are eligible to enter the Induction period 2, AEs that occur before end of Induction Period 1 will be included, even if they occur after dosing ends while they are waiting to enter the next study period
- AEs with an onset date after start of subsequent anti-cancer therapy, after start date of Induction Period 2 treatment, or after the date the decision was made to discontinue treatment as documented in the subject's medical record (i.e. the off-treatment date) will not be included.

6.1.2.2 Induction Period 2

AEs during Induction Period 2 will be defined as those with an onset date time on or after the date-time of the first dose of study treatment in Induction Period 2 (or with an onset date on or after the day of first dose of study treatment in Induction Period 2 if time is not collected or is missing) and not later than discontinuation date from the Induction Period 2

- For subjects who discontinue Induction Period 2 early and enter the Follow-Up Period, AEs with onset after the start of the Follow-Up Phase will not be included, where first day of Follow-Up Phase is defined as the date the decision was made to discontinue treatment as recorded on the off treatment case report form..
- For subjects who discontinue treatment before the end of Induction Period 2 but who are eligible to enter Continuation Period, AEs that occur before end of Induction Period 2 will be included, even if they occur after dosing ends while they are waiting to enter the next studyperiod
- AEs with an onset date after start of subsequent anti-cancer therapy, after start date of Continuation Period treatment, or after the date the decision was made to discontinue treatment as documented in the subject's medical record (i.e. the off-treatment date) will not be included.

6.1.2.3 Induction Period

AEs during the Induction Period will include AEs during both Induction Periods 1 and 2, as defined above.

6.1.2.4 Continuation Period

AEs during Continuation Period will be defined as those with an onset date time on or after the date-time of the first dose of study treatment in the Continuation Period (or with an onset date on or after the day of first dose of study treatment in the Continuation Period if time is not collected or is missing) and not later than discontinuation date from the Continuation Period

AEs with an onset date after start of subsequent anti-cancer therapy, or after the date the decision was made to discontinue treatment as documented in the subject's medical record (i.e. the off-treatment date) will not be included.

6.2 Treatment Regimens

The treatment regimen "**as randomized**" will be retrieved from the IVRS system

- Cohort A: nivolumab followed by ipilimumab
- Cohort B: ipilimumab followed by nivolumab

The treatment regimen "**as treated**" will be the same as the cohort as randomized by IVRS. However, if a subject received the incorrect drugs for **the entire period** of treatment, the subject's treatment regimen will be defined as the incorrect regimen the subject actually received.

6.3 Populations for Analyses

- All Enrolled Subjects: All subjects who signed an informed consent form and were registered into the IVRS.
- All Randomized Subjects: All subjects who were randomized to any cohort in the study. This is the primary dataset for efficacy listings.
- All Treated Subjects: All subjects who received at least one dose of study medication. This is the primary dataset for analysis of study conduct, study population, efficacy, exposure, and safety.

[redacted]

7 STATISTICAL ANALYSES

7.1 General Methods

Unless otherwise noted, the bulleted titles in the following subsections describe tabulations of discrete variables, by the frequency and proportion of subjects falling into each category. Percentages given in these tables will be rounded and, therefore, may not always sum to 100%. Continuous variables will be summarized using the mean, standard deviation, median, minimum and maximum values.

Time to event distribution (e.g. overall survival and duration of response from Week 25) will be estimated using Kaplan Meier techniques. When appropriate, the median along with 95% CI will be estimated based on Brookmeyer and Crowley methodology[3] (using log-log transformation for

constructing the confidence intervals). Rates at fixed time points (e.g. OS at 12 months) will be derived from the Kaplan Meier estimate, and corresponding confidence interval will be derived based on Greenwood formula[4] for variance derivation and on log-log transformation applied on the survivor function S(t).[5] Confidence intervals for binomial proportions will be derived using the Clopper-Pearson method[6].

Unless otherwise noted, tabulations for summary tables will use all treated subjects. However, data from all randomized subjects will be presented in the efficacy listings.

7.2 Study Conduct

7.2.1 Accrual

The accrual pattern will be summarized per country, investigational site, and per month for all enrolled and treated subjects. Randomization date, 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 by cohort and overall in all treated subjects. 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:

- Subjects with baseline ECOG performance status > 1
- Subjects without histologically documented Stage III or Stage IV melanoma, as per AJCC staging system
- Subjects without measurable disease at baseline

On-study:

- Subjects receiving anti-cancer therapy (chemotherapy, hormonal therapy, immunotherapy, standard or investigational agents for treatment of cancer) while on study therapy
- Subjects treated differently than as randomized (subjects who received the wrong treatment, excluding the never treated)

Listings will also be provided for all randomized subjects.

7.3 Study Population

7.3.1 Subject Disposition

The total number of subjects enrolled (randomized or not randomized) will be presented along with the reason for not being randomized. This analysis will be performed on the all enrolled subjects population only.

Number of subjects who discontinued study treatment along with corresponding reason will be tabulated by cohort as treated. Reason for discontinuation will be derived from subject status CRF page. This analysis will be performed only on the all treated subjects population.

Number of subjects randomized but not treated along with the reason will be tabulated by cohort as randomized. This analysis will be performed only on the all randomized subjects population.

A subject listing for all randomized subjects will be provided showing the subject's randomization date, first and last dosing date, off study date and reason for going off-study. A subject listing for subjects not randomized will also be provided, showing the subject's race, gender, age, consent date and reason for not being randomized.

7.3.2 Demographics and Baseline Characteristics

The following baseline characteristics will be summarized by cohort, as treated, for all treated subjects. All baseline presentations will identify subjects with missing measurements. Listings will also be provided for all randomized subjects.

- Age (descriptive statistics)
- Age category I (<65, ≥65)
- Age category II (<65, ≥65- <75, ≥ 75)
- Gender (male, female)
- Race (white, black, Asian, other)
- Baseline ECOG Performance Status (0, 1)
- M Stage at Study Entry (M0, M1a, M1b, M1c)
- AJCC Stage at Study Entry (III, IV)
- Weight (descriptive statistics)
- BRAF mutation status (BRAF mutant, wild type) (source: CRF)
- BRAF mutation test (Cobas+THxID, Other, Unknown)
- Baseline LDH (≤ULN, >ULN)
- Baseline LDH (≤ 2×ULN, >2×ULN)
- History of Brain Metastases (Yes, No)
- Smoking Status (Yes, No)
- Time from Initial Disease Diagnosis to Randomization (<1 year,1-<2 year, 2-<3 year,3- <4 year, 4-<5 year, ≥5 year)
- All lesions (Investigator Tumor Assessments at Baseline): sites of disease, number of disease sites per subject.
- Target lesions (Investigator Tumor Assessments at Baseline): Presence of target lesions, site of target lesion, sum of longest diameter of target lesion.

7.3.3 Medical History

General medical history will be listed by subject.

7.3.4 Prior Therapy

The following will be summarized by cohort for all treated subjects as treated.

- Prior neo-adjuvant therapy (yes/no)

- Prior adjuvant therapy (yes/no)
- Time from completion of prior adjuvant therapy to randomization (subjects who received prior adjuvant therapy), (< 6 months and >= 6 months)
- Prior surgery related to cancer (yes/no)
- Prior radiotherapy (yes/no)

Agents and medication will be reported using the generic name. A listing by subject will also be provided for all randomized subjects.

7.3.5 Baseline Examinations

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

7.4 Extent of Exposure

Analyses will be performed by treatment group "as treated" in all treated subjects, unless otherwise specified.

7.4.1 Administration of Study Therapy

The following parameters will be summarized (descriptive statistics) by cohort:

- Time from randomization to first dose of study therapy (0 to 3 days, > 3 to 7, > 7 to 14, > 14 to 21, > 21 to 28, > 28)

The following parameters will be summarized (descriptive statistics) by study therapy and cohort over the entire study treatment period and also separately for the Induction Period and the Continuation Period:

- Number of doses received (nivolumab and ipilimumab):
- Cumulative dose (nivolumab and ipilimumab)
- Relative dose intensity (%) using the following categories: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%. (nivolumab and ipilimumab)

Duration of treatment will be presented by cohort using a Kaplan-Meier curve whereby the last dose date will be the event date for those 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 dosing of study medication (record of study medication, infusion details, and dose changes) and a listing of batch numbers will be also provided.

Table 7.4.1-1: Study Therapy Parameter Definitions

	Nivolumab	Ipilimumab
Dosing schedule per protocol	3 mg/kg every 2 weeks	3 mg/kg every 3 weeks for 4 doses
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	Dose (mg/kg) is defined as Total Dose administered (mg)/Most recent weight (kg). Dose administered in mg at each dosing date and weight

Table 7.4.1-1: Study Therapy Parameter Definitions

	Nivolumab	Ipilimumab
	are collected on the CRF.	are collected on the CRF.
Cumulative Dose	Cum dose (mg/kg) is sum of the Nivolumab doses (mg/kg) administered to a subject.	Cum dose (mg/kg) is sum of the Ipilimumab doses (mg/kg) administered to a subject.
Relative Dose Intensity (%)	<u>For subjects treated with nivo-ipi (Cohort A) sequence and entering Continuation Period:</u> Cum dose (mg/kg) /[(Last dose date of Induction Period Nivolumab - Start dose date of Induction Period Nivolumab + 14 + Last dose date of Continuation - Start dose date of Continuation + 14) x 3 /14] x 100 <u>For all other subjects:</u> Cum dose (mg/kg) /[(Last Nivolumab dose date - Start Nivolumab dose date + 14) x 3 /14] x 100	Cum dose (mg/kg)/[(Last Ipilimumab dose date - Start Ipilimumab dose date + 21) x 3/21] x 100
Duration of treatment	Last dose date - Start dose date +1	Last dose date - Start dose date +1

7.4.2 Modifications of Study Therapy

7.4.2.1 Dose Delays

Dose delays are not permitted during the Induction Period for either nivolumab or ipilimumab. However, dosing delays are allowable if the subject is in the Continuation portion of the trial.

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). Reason for dose delay will be retrieved from CRF dosing pages.

The following parameters will be summarized by Cohort for the Continuation Period:

- Number of dose delays per subject, length of delay, and reason for dose 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 summarized by cohort per study therapy:

- 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 and Discontinuations

Each nivolumab or ipilimumab dose can be omitted. If dosing is interrupted > 6 weeks, the subject must be permanently discontinued from study treatment with that particular drug, except as specified in Section 4.3.6.2 of the protocol. This information will be retrieved from CRF dosing pages.

The following parameters will be summarized by cohort per study therapy separately for the Induction Period and the Continuation Period:

- Number of subjects with at least one dose omission, the reason for omission, and the number of dose omissions per subject.
- Number of subjects with at least one drug discontinuation and the reason for discontinuation

[redacted]

7.5 Efficacy

7.5.1 Response Rate at Week 25

Response rate at Week 25 will be computed by cohort using all treated subjects. Response rate estimates and corresponding 95% CIs will be calculated using the Clopper-Pearson method[6].

7.5.1.1 Sensitivity analysis

Two separate sensitivity analyses of response rate at Week 25 will be performed using the following modifications:

- The analysis population will be restricted to those subjects who had at least one dose of study medication in Induction Period 2 and were response evaluable at Week 25 (i.e., those subjects who actually had a tumor assessment at Week 25 as defined in Table 8.1-1).
- An analysis using all treated subjects will be performed where evaluations occurring after the date of tumor-directed radiotherapy or tumor-directed surgery will be included when determining or confirming response at Week 25. Evaluations occurring after the date of all other types of subsequent anticancer therapy listed in Section 7.5.3.2 will still be excluded.

7.5.1.2 Further Characterization of Response Rate at Week 25

Response at Week 25 will be further characterized in all treated subjects as follows:

DOR from Week 25 will be summarized for subjects with confirmed response at Week 25 using the Kaplan-Meier (KM) product limit method for each cohort. Median DOR, corresponding two-sided 95% CIs, and range will also be calculated. In addition, the percentage of responders still in response at different time points (3, 6 and 12 months) will be presented based on the KM plot. Minimum follow-up must be longer than the time point to generate the rate.

7.5.2 Progression Rates at Weeks 13 and 25

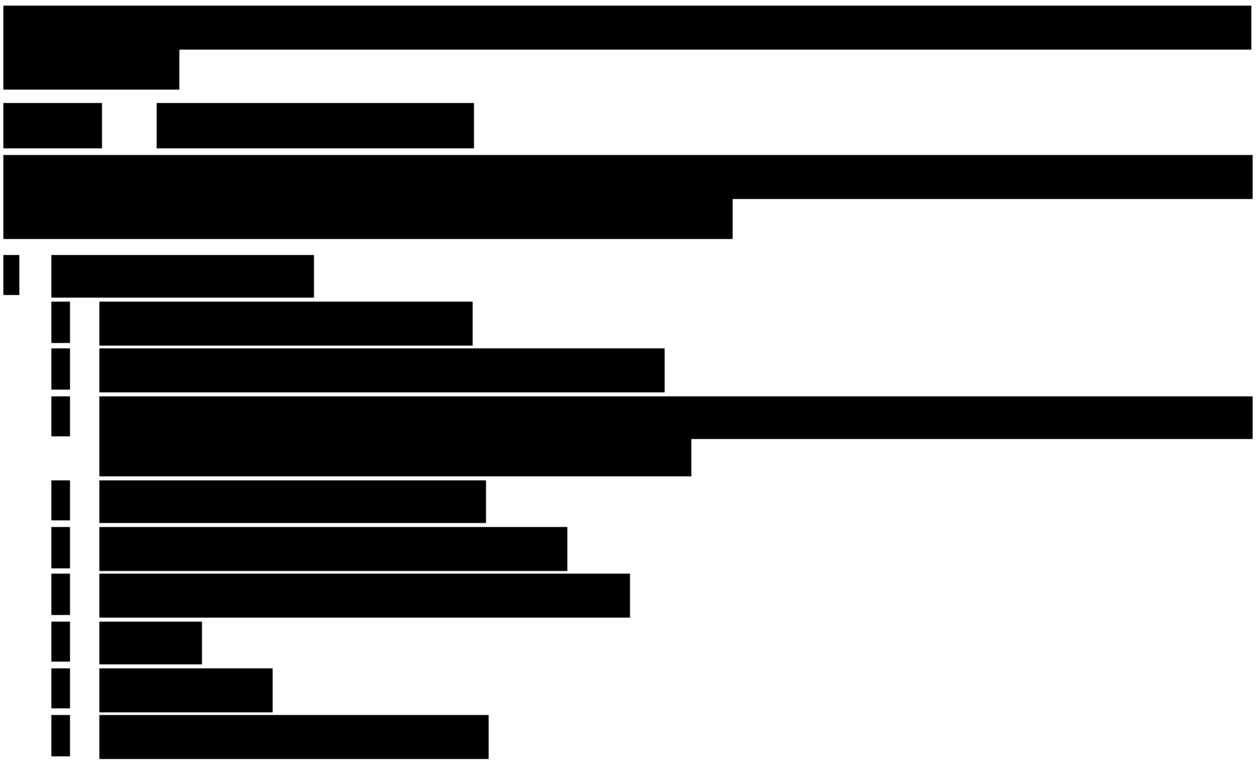
Progression rates at Week 13 and at Week 25 will be computed by cohort using all treated subjects. Progression rate estimates and corresponding 95% CIs will be calculated using the Clopper-Pearson method.

7.5.2.1 Sensitivity analyses

Sensitivity analyses of progression rates at Weeks 13 and 25 will be performed using the following modifications:

- The analysis population will be restricted to those subjects who were still on treatment at the specified study week and actually had a tumor assessment at the specified study week as defined in Table 8.1-1
- An analysis using all treated subjects will be performed where evaluations occurring after the date of tumor-directed radiotherapy or tumor-directed surgery will be included when determining progression at Week 13 or Week 25. Evaluations occurring after the date of all other types of subsequent anticancer therapy listed in Section 7.5.3.2 will still be excluded.

[redacted]



7.5.4 Other Efficacy Analyses

The following subject-level graphics will also be provided by cohort as treated:

- For all treated subjects, time courses of the following events of interest will be graphically displayed: treatment period, tumor response, progression, treatment-related grade 3-5 AEs, last dose received, and death.

7.5.5 Interim Analysis

Interim analyses of efficacy endpoints may be performed to support submission and publication needs.

7.6 Safety

Unless otherwise specified, safety summary tables will be generated for all treated subjects following the definition of on-treatment as described in Section 6.1.2. Summaries will be performed by cohort "as treated". A subset of safety endpoints will also be summarized separately by study period (Induction Period 1, Induction Period 2, and Continuation Period, as defined in Sections 6.1.2.1, 6.1.2.2, and 6.1.2.4, respectively). These additional summary tables are described in Section 7.6.15. Listings will include all available data

7.6.1 Treatment-Related Grade 3-5 AEs during the Induction Period

For the analysis of the primary endpoint (rate of treatment-related Grade 3-5 AEs during the Induction Period), a treatment-related AE will be a drug-related AE as defined in the CORE Safety SAP[2] . Per the CORE Safety SAP, 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.

7.6.1.1 Primary Analysis

Rate of treatment-related Grade 3-5 AEs during the Induction Period (as defined in Section 6.1.2.3) will be computed by treatment cohort using all treated subjects. Corresponding 95% CIs will be calculated using the Clopper-Pearson method.

7.6.1.2 Sensitivity Analysis

As sensitivity analysis, rates and 95% CI will be also computed using the subset of subjects who received at least one dose of study treatment in Induction Period 2.

7.6.1.3 Further Characterization of Treatment-Related AEs During the Induction Period

An overall summary of drug-related AEs during the Induction Period by worst CTC grade (any grade, grade 3-4, grade 5) will be presented by system organ class (SOC) and preferred term (PT) for all treated subjects in each cohort. Additional summaries of drug-related AEs will be provided separately by study period (Induction Period 1, Induction Period 2, and Continuation Period) as described in Section 7.6.15.

7.6.2 Deaths

See CORE Safety SAP[2].

7.6.3 Serious Adverse Events

See CORE Safety SAP[2].

7.6.4 Adverse Events Leading to Discontinuation of Study Therapy

See CORE Safety SAP[2].

7.6.5 Adverse Events Leading to Dose Modification

See CORE Safety SAP[2].

7.6.6 Adverse Events

See CORE Safety SAP[2].

7.6.7 Multiple Events

See CORE Safety SAP[2].

7.6.8 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). These categories 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 Medical Dictionary for Regulatory Activities (MedDRA).

For information, the following 7 categories of select AEs have been defined at the time of finalization of this SAP: Endocrine AEs, Hypersensitivity/Infusion Reactions, Gastrointestinal AEs, Hepatic AEs, Pulmonary AEs, Renal AEs, and Skin AEs.

The final list used for the clinical study report (CSR) will be included in an Appendix of the CSR.

See CORE Safety SAP[2] for a detailed description of the analyses to be conducted for select AEs.

Furthermore, in order to characterize the evolution of events that were ongoing from the first induction period into the second induction period, an additional by subject listing of select AEs by cohort and select AE category will be provided. The following information will be presented for each reported select AE: current treatment at AE onset, study period at AE onset, study visit at AE onset, date/time and study day of AE onset, AE resolution date/time, duration of event, time of AE onset relative to most recent dose, type of event (serious or non serious), SOC, PT, reported term, relationship to study drug, CTC grade, treatment required (yes or no), and action taken.

7.6.9 Immune Modulating Medication

See CORE Safety SAP[2].

7.6.10 Clinical Laboratory Evaluations

7.6.10.1 Hematology

See CORE Safety SAP[2].

7.6.10.2 Serum Chemistry

Amylase and lipase will be summarized in addition to the serum chemistry parameters described in the CORE Safety SAP[2].

7.6.11 Vital Signs and Pulse Oximetry

See CORE Safety SAP[2].

7.6.12 Immunogenicity

Immunogenicity analyses will be performed separately for Nivolumab ADA Evaluable Subjects and Ipilimumab ADA Evaluable Subjects. See CORE Safety SAP[2].

7.6.13 Pregnancy

See CORE Safety SAP[2].

7.6.14 Clinical Safety Program

See CORE Safety SAP[2].

7.6.15 Other Safety Analyses

The following additional safety summaries will be presented by cohort separately for Induction Period 1 using subjects treated in Induction Period 1, Induction Period 2 using subjects treated in

Induction Period 2, and Continuation Period using subjects treated in Continuation Period, where study periods are as defined in Sections 6.1.2.1, 6.1.2.2, and 6.1.2.4.

Adverse Events

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

Serious Adverse Events

- Overall summary of SAEs by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by SOC/PT

Adverse Events Leading to Discontinuation of Study Therapy

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

Select Adverse Events

- Overall summary of any select AEs by worst CTC grade presented by Category/PT (any grade, grade 3-4, grade 5)

An additional summary by cohort of drug-related AEs by worst CTC grade during Induction Period 2 will be performed excluding AEs persisting from Induction Period 1 that are downgraded in Induction Period 2 compared to last grade observed in Induction Period 1.

7.6.16 Interim Analyses

Additional interim analyses of safety endpoints may be performed to support submission and publication needs. In particular, an interim database lock and release of randomized treatment codes will be performed to support a drug manufacturing process biocomparability assessment for nivolumab. For this purpose, the following summaries will be produced:

- Overall summary of any AE during Induction Period 1 by worst CTC grade, presented by SOC/PT for all treated subjects in Cohort A
- Overall summary of any drug-related AE during Induction Period 1 by worst CTC grade, presented by SOC/PT for all treated subjects in Cohort A
- Overall summary of any hypersensitivity/infusion-related select AEs during Induction Period 1 by worst CTC grade, presented by PT for all treated subjects in Cohort A
- Listing of all AEs for all treated subjects in Cohort A

[redacted]

[redacted]

[redacted]

[redacted]

7.9 Outcomes Research

Not applicable.

8 CONVENTIONS

8.1 Study Day Intervals

For the summaries of response rates and progression rates at a specific week, Table 8.1-1 shows the classification of study day intervals that will be used. The variable "Week" is defined using the number of days since the beginning of study dosing in Induction Period 1. The first day of dosing in Induction Period 1 is defined as "Day 1".

Table 8.1-1: Study Day and Visit Windows

Week	Target Day[a]	Study Day Interval[a]
13	85	71 - 100
25	169	155 - 184
33	Next tumor assessment following the Week 25 assessment	Date of Week 25 Assessment + 28 days - end of study

[a] measured from first day of dosing in Induction Period 1

If a subject has more than one measurement included within a study day interval, then the assessment closest to the target day will be the measurement used in the analysis. In case of ties between the number of days between the day of the measurement and the target day for observations located before and after the target day, the earlier assessment will be used.

Evaluations occurring after the date of subsequent anticancer therapy will not be included when determining or confirming response at Week 25 or when determining progression at Week 13 or Week 25. Unless specified otherwise in a particular analysis, subsequent anticancer therapy

encompasses all interventions listed in Section 7.5.3.2, including tumor-directed radiotherapy and tumor-directed surgery.

8.2 Imputation of Missing response or progression evaluations

Response Rate at Week 25

If a treated subject is missing their tumor assessment at Week 25, due to early discontinuation or because the assessment falls outside the study day interval defined in Table 8.1-1, then this subject will be counted as a non-responder for purposes of the main analysis of response rate at week 25. A sensitivity analysis will also be performed that only includes subjects who had at least one dose of study medication in Induction Period 2 and who actually had a tumor assessment at Week 25 as defined in Table 8.1-1.

Progression Rate at Week 13 and Week 25

If a treated subject is missing their tumor assessment at the specified study week due to early discontinuation or because the assessment falls outside the study day interval defined in Table 8.1-1, then the results of the previous tumor response evaluation will be carried forward for purposes of the main analysis of progression rates at Week 13 and Week 25. For example, if a subject discontinued due to PD prior to week 13, then this subject will be counted as having PD at week 13 for purposes of analysis. Both clinical and radiological progressions will be counted as a progression outcome. Subjects who die without a reported prior progression will be considered to have progressed on the date of their death.

8.3 Imputation of Missing and Partial Dates

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

For missing and partial adverse event onset dates, imputation will be performed using the Adverse Event Domain Requirements Specification[7]. Missing and partial Non-Study Medication Domain dates will be imputed using the derivation algorithm described in 4.3.3 of BMS Non-Study Medication Domain Requirements Specification[8].

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 cases where 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 may 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 to first dosing date, duration of response, and time to response) will be calculated as follows: Duration = (Last date - first date + 1)

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

9 CONTENT OF REPORTS

All analyses described in this SAP will be included in the Clinical Study Report(s) except where otherwise noted. Refer to the Data Presentation Plan for mock-ups of all tables and listings.

[redacted]