STATISTICAL ANALYSIS PLAN
FOR MELANOMA

AN EXPLORATORY STUDY OF THE BIOLOGIC EFFECTS OF NIVOLUMAB AND NIVOLUMAB IN COMBINATION WITH IPILIMUMAB TREATMENT IN SUBJECTS WITH ADVANCED MELANOMA (UNRESECTABLE OR METASTATIC)

PROTOCOL(S) CA209038

VERSION # 2.1

Official Title of Study:

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

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Research Hypothesis:

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

Schedule of Analyses:

Final Analysis will be performed after all subjects have completed the study (after the follow-up periods) or discontinued prematurely.

Administrative interim analyses on safety, efficacy, pharmacokinetics (PK), immunogenicity, and selected biomarkers may be performed at various times prior to study completion in order to inform subsequent parts of the study, facilitate program decisions, and to support scientific

publications or presentations. Therefore, data may be reviewed prior to the final lock of the study database. No formal inferences requiring any adjustment to statistical significance level will be performed. Additional survival analysis may be performed beyond analysis for the final Clinical Study Report (CSR).

2 STUDY DESCRIPTION

2.1 Study Design

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

Approximately 150 subjects with advanced melanoma (unresectable or metastatic) will be treated in this study in four (4) parts.

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

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

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

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

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

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

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

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

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

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

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

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

2.2 Treatment Assignment

All enrolled subjects will be assigned a subject number. The subject number will be assigned through an interactive voice response system (IVRS) once the subject signs informed consent.

Enrolled subjects meeting all eligibility criteria will be assigned to Cohort 1 or 2 depending on prior anti-CTLA4 therapy status. After Amendment 04, enrolled subjects meeting all eligibility criteria will be assigned to Arm A for Part 2. After the optimal timing of the biopsy has been determined in Part 2 then, enrolled subjects meeting all eligibility criteria will be randomly assigned to Arms A or B in a 2:1 ratio in Part 3. In parallel, enrolled subjects meeting all eligibility criteria will be randomly assigned to Arms D or E in a 1:1 ratio in Part 4.

2.3 Blinding and Unblinding

This is an open label study.

[redacted]

3 OBJECTIVES

3.1 Primary

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

3.2 Secondary

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

3.3 [redacted]

4 ENDPOINTS

4.1 Primary Endpoints

The primary objective of the study is to investigate the pharmacodynamic activity of biomarkers as measured by changes from baseline in biomarkers such as activated and memory T cells, interferon, interferon inducible factors, and CD4 and CD8 T cells infiltration. The endpoints are summarized in Table 4.1-1. Some biomarker endpoints listed below may be subject to change as technologies and assay evolve and based on data availability.

Table 4.1-1: Primary Biomarker Endpoints

Endpoints	Assay	Source
Percent change (or change) from baseline of Activated T cell (HLA-DR+, ICOS+ CD4 and CD8 T cells)	Flow cytometry	Blood sample /PBMC
Percent change (or change) from baseline of Memory T cell (CCR7-CD45RA-CD27+CD28+ and CCR7+CD45RA-CD27+CD28+ CD4 and CD8 T cells)	Flow cytometry	Blood sample /PBMC
Percent change (or change) from baseline of Interferon and interferon gamma inducible factors (IFN-gamma, CXCL9, CXCL10)	Multiplex-based assay method	Blood sample

Table 4.1-1: Primary Biomarker Endpoints

Endpoints	Assay	Source
Percent change (or change) from baseline of T cell infiltration (CD3, CD4 and CD8)	Immunohistochemistry	Tumor tissue

4.2 Secondary Endpoints

4.2.1 Safety and Tolerability

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

- Incidence rate of adverse events (AEs), serious adverse events (SAEs), select AEs, AEs leading to discontinuation, and deaths.
  - All non-serious AEs will be assessed from the start of dosing.
  - All SAEs and deaths will be assessed from the date of the subject's written informed consent.
  - All AEs (serious and non-serious), and deaths will be assessed up to 100 days after the subject's last dose of study drug or until they discontinue the study as per Protocol Section 3.1[2].
  - Select AE categories are captured in Table 11-3 of the core safety SAP for CA209[3]. This list is subject to change and may not necessarily reflect the categorizations at each database lock. A separate listing will be provided for the categorizations at each analysis.
  - Immune modulating AEs may also be summarized
- Occurrence of clinical laboratory test abnormalities including hematology and serum chemistry abnormalities will be examined.
- Vital signs: Changes in vital signs relative to baseline including blood pressure and heart rate measurements.
- Other safety endpoints include changes in or incidence of: weight, height, Eastern Cooperative Oncology Group (ECOG) performance status, electrocardiogram abnormalities, and O_2 saturation (pulse oximetry).

Adverse events will be categorized using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA) at the time of each database lock; both AEs and laboratory values will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

4.2.2 Preliminary Anti-tumor Activity

The secondary objective relating to efficacy is to describe the anti-tumor activity of nivolumab and nivolumab in combination with ipilimumab in subjects with advanced melanoma. Changes in tumor measurements and tumor response will be measured based on RECIST 1.1. Disease evaluation will be performed at baseline, and then prior to each cycle for Part 1, or prior to the

first dose of the next treatment visit for Parts 2-4, approximately every 8 weeks until confirmed disease progression or treatment discontinuation, whichever happens later. Patients will be followed for overall survival up to 2 years from the first dose of study medication or for those patients that enter the Extension Period, overall survival assessments will be continued for 100 days following the last treatment dose. The following set of efficacy study-level endpoints will be used:

- **Objective Response Rate (ORR)**: The total number of subjects whose best overall response (BOR) is either a complete response (CR) or partial response (PR) divided by the total number of subjects in the population of interest (eg, all treated subjects or response-evaluable subjects).
  - Best Overall Response: The subject's best response designation over the study as a whole, recorded between the date of first study drug administration and the date of objectively documented progression per RECIST 1.1, with subsequent confirmation, or date of subsequent anti-cancer therapy, whichever occurs first in the study.
    - For those subjects who have surgical resection, only pre-surgical tumor assessments will be considered in the determination of BOR.
    - For subjects without documented progression per RECIST 1.1 or subsequent anti-cancer therapy, all available response designations will contribute to the BOR determination.
    - For subjects who continue treatment beyond progression, the BOR should be determined based on response designations recorded up to the time of the initial RECIST 1.1 defined progression.
    - For a BOR of CR or PR, the response assessment must have been confirmed by a consecutive assessment meeting the criteria for response and performed no less than 4 weeks (28 days) after the criteria for response are first met.
    - For a BOR of stable disease (SD), the following criteria will be applied to the SD derivation:
      - The minimum criteria for SD duration (6 weeks) must have been satisfied (considering the ± 1 week tumor assessment window, 35 days will be used to derive SD).
- **Median Duration of Response (mDOR)**: The significance of ORR is assessed by its magnitude and duration of response.
  - Duration of Response: DOR will be calculated for subjects with BOR of CR or PR only, and is defined as time between the date of first documented objective response and the date of the first subsequent disease progression or death, whichever occurs first, if death occurred within 100 days after last dose of study medication.
    - Subjects whose death occurred more than 100 days after last dose without prior progression will be censored at the last tumor assessment date (prior to subsequent therapy).
    - Subjects who remain alive and have not progressed will be censored on the last tumor assessment date (prior to subsequent cancer therapy).

- Subjects who receive subsequent therapy prior to documented disease progression, DOR will be censored on the date of last tumor assessment prior to subsequent therapy.

- **Median Time to Response (mTTR)**: The objective response will be further characterized by the time to response.
  - Time to Response (TTR): The TTR for a subject with a BOR of CR or PR is defined as the time from the first dosing date to the date of the first documented objective response (CR or PR).
    - TTR will only be evaluated in subjects with a BOR of CR or PR.
- **Progression Free Survival Rate (PFSR) at Week t**: The proportion of subjects remaining progression free and surviving to time t, where t is a specific length of time, eg, 24 weeks, which will be determined by the available data for each interim or final analysis and will be documented in the data presentation plan (DPP). The proportion will be calculated by the product-limit method (Kaplan-Meier estimate) which takes into account censored data.
  - Progression Free Survival (PFS): The PFS for a subject is defined as the time from the date of first dose of study medication to the date of the first documented disease progression, or death due to any cause, whichever occurs first, if death occurred within 100 days after last dose of study medication.
    - Subjects who die within 100 days after last dose without a reported prior progression will be considered to have progressed on the date of their death.
    - Subjects whose death occurred more than 100 days after last dose of study medication without prior progression will be censored at the last tumor assessment date (prior to subsequent therapy).
    - Subjects who remain alive and have not progressed will be censored on the last tumor assessment date (prior to subsequent cancer therapy).
    - Subjects who did not have any on study tumor assessment and did not die within 100 days after last dose of study medication will be censored on the date of first dose of study medication.
    - Clinical deterioration in the absence of radiographic evidence is not considered progression for the purpose of determining PFS when using objectively documented progression.
- **Overall Survival Rate (OSR) at Month t**: The proportion of subjects surviving to time t, where t is a specific length of time, eg, 12 months, which will be determined by the available data for each interim or final analysis and will be documented in the DPP. The proportion will be calculated by the product-limit method (Kaplan-Meier estimate) which takes into account censored data.
  - Overall Survival (OS): The OS for a subject is defined as the time from the date of first dose of study medication to the date of death for any cause.
    - A subject who has not died will be censored at last known date alive.

Note: For the final CSR, investigator assessed BOR, response date and progression date (as recorded on corresponding case report form [CRF]) will be used to derive efficacy endpoints.

For administrative interim analysis (or analyses), BMS internal derived BOR, response date and progression date will be used to derive efficacy endpoints (investigator assessed BOR, response date and progression date are usually missing at the time of interim analyses).

[redacted]

[redacted]

5 SAMPLE SIZE AND POWER

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

Table 5-1: Probability that estimated ratio of on-treatment to baseline value is within 20% of true value

Intra-subject Standard Deviation (log-scale)	0.2	0.3	0.4	0.5	0.6	0.7	0.8
Probability	100%	100%	97%	93%	86%	80%	74%

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

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

It is of interest to ensure precision of the estimate of the proportion of subjects with increased activated T cell on-treatment (at optimal window for biopsy) in part 2 and part 3 Arms A-C. With a total of 30 subjects (from part 2 and 3) treated in Arm A (with biopsy collected at optimal on-treatment window), the maximum width of the exact 2-sided 95% confidence interval (CI) is 37% when the proportion of subjects with increased activated T cells is expected to be in the 20% to 60% range. The 95% exact CIs are presented in Table 5-2.

Table 5-2: 95% Exact CI for Proportion of Subjects with Increased Activated T cell On-treatment

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

With a total of 10 subjects treated in Arm B (with biopsy collected at optimal on-treatment window), the maximum width of the exact 2-sided 95% CI is 59% when the proportion of subjects with increased activated T cells is expected to be in the 20% to 30% range. The 95% exact CIs are presented in Table 5-3.

Table 5-3: 95% Exact CI for Proportion of Subjects with Increased Activated T cell On-treatment

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

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

Approximately, 10 subjects will be treated in Arm D and 10 subjects in Arm E to provide additional information regarding pharmacodynamic activity of immunomodulatory biomarkers

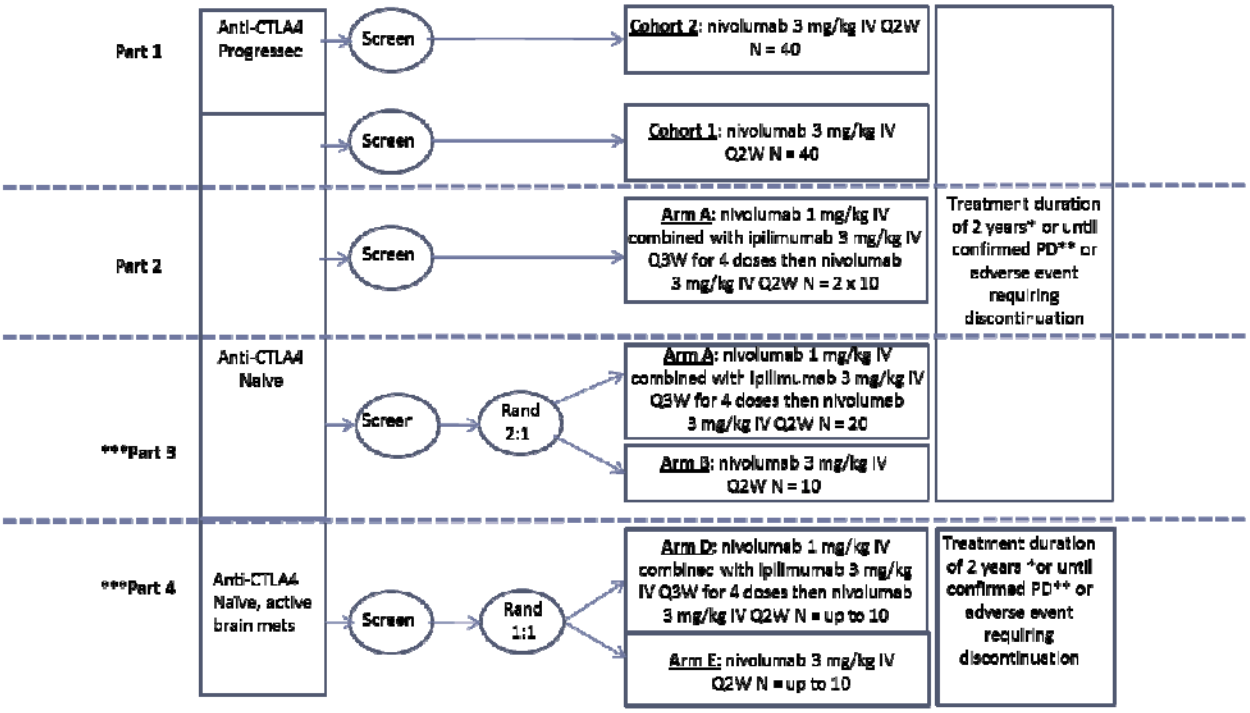
following treatment with nivolumab and nivolumab in combination with ipilimumab. Administration of nivolumab or nivolumab in combination with ipilimumab to 10 subjects per arm provides 90% probability of observing at least one occurrence of any adverse event (or one response) that would occur with a 21% incidence in the population from which the sample is drawn.

6 STUDY PERIODS, TREATMENT REGIMENS, AND POPULATIONS FOR ANALYSES

6.1 Study Periods

Subjects will complete up to four periods of the study (Screening, Treatment, Follow-up, and Survival Follow-up). A study schematic is presented in Figure 6.1-1.

Figure 6.1-1: Study Schematic



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

**Subjects may be treated beyond PD, refer to Protocol[2] Section 4.3.8.

6.1.1 Screening Period

Subjects will go through a screening period of no longer than 28 days. Screening period begins by establishing the subject's initial eligibility and signing of the informed consent form (ICF). Subject is enrolled using the Interactive Voice Response System (IVRS).

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 date of the first dose of study treatment.
- Baseline evaluations for vital signs (including ECOG status), pulse oximetry, and ECG will be defined as evaluations with a date on or prior to the date of first dose of study treatment, since these procedures are to be performed prior to dosing as specified in Protocol Section 5.3 and Tables 5.1B, D, and E[2].
- Baseline evaluations for laboratory values will also be defined as evaluations with a date on or prior to the date of first dose of study treatment, in an alignment with the core safety SAP for CA209[3].

If there are multiple valid assessments at baseline, then the assessment that is closest to the date (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), then the assessment with the latest database entry date (and time, if collected will be considered as baseline.

6.1.2 Treatment Period

Nivolumab will be given every 2 weeks when administered as monotherapy (Cohorts 1 and 2; Arms B and E; Arms A, C, and D after stopping ipilimumab) and every 3 weeks when administered in combination therapy with ipilimumab. Ipilimumab will be given every 3 weeks when administered as monotherapy (Arm C) or combination therapy (Arms A and D).

On days where both study drugs are given, nivolumab will be given first followed by ipilimumab and will start no sooner than 30 minutes after completion of the nivolumab infusion and after the post-nivolumab pharmacokinetic blood sample is drawn.

The treatment period is defined as starting from the date and time of the first dose of study medication. The treatment period ends 14 days after the last dose of nivolumab, if the last dose is nivolumab, and 21 days after the last dose of ipilimumab, if the last dose is ipilimumab.

6.1.3 Follow-up Period

The follow-up period begins 15 days after the last dose of nivolumab, if the last dose is nivolumab, and 22 days after the last dose of ipilimumab, if the last dose is ipilimumab.

Each patient will continue in follow-up for a maximum period of up to 100 days; follow-up office visits 1 and 2 (40-60 days and 101-120 days after the stop of study therapy).

6.1.4 Survival Follow-up Period

All patients who do not enter the Extension Period will be followed for overall survival assessment every 3 months up to 2 years from the first dose of study therapy.

6.1.5 Extension Period

At the completion of 2 years of therapy, those subjects who are benefiting and still meet study criteria may continue after discussion and agreement between the investigator and Medical Monitor and will enter the Extension Period. Patients that enter the Extension Period will be followed for overall survival assessments up to a maximum of 100 days after the last treatment dose.

6.2 Treatment Regimens

Treatment administration for nivolumab and ipilimumab (a ± 2-day window will be allowed) is provided in Table 6.2-1.

The treatment group "as assigned" will be retrieved from the IVRS system for subjects who were assigned (Parts 1 and 2) or randomized (Parts 3 and 4) to a group. The treatment group "as treated" is expected to be the same as the arm as randomized by IVRS. However, if a subject received the incorrect drug for the entire period of treatment, this will be documented as a relevant protocol deviation (see Section 7.2.3) and the subject's treatment group will be defined as the incorrect drug the subject actually received. For example, if a subject was randomized to the combination therapy, but only received nivolumab monotherapy for the entire treatment duration, they will be put into the nivolumab monotherapy treatment group.

6.3 Populations for Analyses

- 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 medication
- Pharmacokinetic Subjects: All subjects who received at least one dose of study medication and have available serum concentration data
- Response Evaluable Subjects: All treated subjects with measurable disease at baseline and one of the following: 1) at least one post-baseline tumor assessment, 2) clinical progression, or 3) death (if death occurred within 100 days after last dose of study medication)
- Immunogenicity Subjects:
  - Nivolumab ADA Evaluable Subjects: All treated subjects with baseline and at least 1 post-baseline nivolumab immunogenicity assessment.
  - Ipilimumab ADA Evaluable Subjects: All treated subjects with baseline and at least 1 post-baseline ipilimumab immunogenicity assessment.
- Biomarker Evaluable Subjects: All Treated Subjects with at least one evaluable measurement for a specific marker will be included in the dataset for that marker. Evaluable may differ depending on the analysis.

Table 6.2-1: Treatment Administration

Cohort/ Arm	Dose	Infusion Time	Population
1 and 2	3 mg/kg nivolumab every 2 weeks	60 minutes	**Cohort 1**: ~40 anti-CTLA4 naive subjects **Cohort 2**: ~40 anti-CTLA4 progressed subjects
A	1 mg/kg nivolumab + 3 mg/kg ipilimumab every 3 weeks x 4 doses And then 3 mg/kg nivolumab	**Part 2**: nivolumab 60 minutes + 30 minutes break + ipilimumab 90 minutes And then nivolumab 60	Anti-CTLA4 naive only ~10 subjects with biopsy window between Days 8 and 15 ~10 subjects with biopsy

Table 6.2-1: Treatment Administration

Cohort/ Arm	Dose	Infusion Time	Population
	every 2 weeks	minutes	window between Days 22 and 29
		Part 3: nivolumab 30 minutes + 30 minutes break + ipilimumab 30 minutes And then nivolumab 30 minutes	Anti-CTLA4 naive only ~20 reduced infusion subjects
B	3 mg/kg nivolumab every 2 weeks	30 minutes	Anti-CTLA4 naive only ~10 reduced infusion subjects
D	1 mg/kg nivolumab + 3 mg/kg ipilimumab every 3 weeks x 4 doses And then 3 mg/kg nivolumab every 2 weeks	Nivolumab 30 minutes + 30 minutes break + ipilimumab 30 minutes And then nivolumab 30 minutes	Anti-CTLA4 naive only ~10 reduced infusion subjects with brain metastases
E	3 mg/kg nivolumab every 2 weeks	30 minutes	Anti-CTLA4 naive only ~10 reduced infusion subjects with brain metastases

7 STATISTICAL ANALYSES

7.1 General Methods

All analysis will be performed in SAS (Statistical Analysis System software, SAS Institute, North Carolina, USA) using version 9.2 or higher. Some figures may be generated using S-Plus.

Continuous variables will be summarized using descriptive statistics, ie, medians, minimums, maximums and means with standard deviations/standard errors of the mean. Some continuous variables may also be summarized using the geometric mean and coefficient of variation. Categorical variables will be summarized by frequencies and percentages. Percentages will be rounded and, therefore, may not always add up to 100. Percentages less than 0.1 will be indicated as "< 0.1".

Statistical analyses will be presented by part, cohort, or arm as defined in Figure 6.1-1 and Table 6.2-1. Based on the comparability of data in each part, cohort, or arm, any of the groups may be combined to increase the number of subjects for analyses. The grouping schemes for analyses are further described in the DPP.

7.2 Study Conduct

7.2.1 Study Information

Listing:

- Batch number will be listed by batch number and subject. It is noted that a subject may appear multiple times under different batch numbers.

- Randomization code by site will be provided for parts of the study which are randomized (Parts 3 and 4).

7.2.2 Accrual

The following will be presented on the All Enrolled Subjects.

Summary:

- Number (%) of subjects accrued by country and investigational site

Listing:

- Subjects accrued by country and investigational site

7.2.3 Relevant Protocol Deviations

A relevant protocol deviation is a deviation from the protocol which is programmed in the database and which could potentially affect the interpretability of the study results. Non-programmable relevant eligibility and on-treatment protocol deviations, as well as significant (both programmable and non-programmable) will be reported through ClinSIGHT listings. The following programmable deviations will be considered as relevant protocol deviations and a listing will be provided. During the conduct of the trial, if any relevant protocol deviation is discovered that is not on this list, this SAP should be amended prior to the final database lock. Relevant protocol deviations, their implications, and subsequent actions will be reported in the CSR.

At Entrance:

- Subject enrolled to Cohort 1 and Arms A, B, D, and E and received prior anti-CTLA4 therapy (Inclusion Criteria 2.a.iii).
- Subjects enrolled to Cohort 2 and did not receive prior anti-CTLA4 therapy (Inclusion Criteria 2.a.iv).
- Subjects without measurable disease at baseline (Inclusion Criteria 2.d).
- Subjects with baseline ECOG performance status > 1 (Inclusion Criteria 2.f) at the screening visit only.
- Subjects enrolled in Parts 2, 3, and 4 without BRAF V600 mutation status (Inclusion Criteria 2.i).
- Subjects who have anti-cancer therapy (eg, chemotherapy, biologics, vaccines, radiotherapy, or hormonal treatment) within 4 weeks of study drug administration (Exclusion Criteria 5.c).
- Subjects whose baseline assessments (particularly efficacy assessments) are more than 28 days prior to the start of study therapy

On-Treatment:

- Subjects receiving anti-cancer therapy (chemotherapy, hormonal therapy, immunotherapy regimens, or radiation therapy, standard or investigational) before the last dose of study drug
  - In the event that this occurs, this will be treated as subject's subsequent therapy for certain efficacy assessments described in Section 4.2.2.
- Subjects receiving treatment that is different than what they were assigned or randomized

  - In the event that this occurs, subjects will be grouped with the actual received treatment (instead of assigned or randomized treatment) for the analyses.
- For Part 2, subjects whose on-treatment biopsy day relative to the start of study therapy is considerably different than the biopsy window which they were assigned.
  - In the event that this occurs, subjects would be grouped with their actual biopsy window (instead of assigned), or they would be excluded from the grouping schemes comparing the biopsy windows if their on-treatment biopsy is outside the 2 allowable windows.
- During the first dosing visit, if subjects receive ipilimumab dose first, before receiving the nivolumab dose during a visit which a combination therapy is planned.
- Subjects receiving immunosuppressive agents during the course of treatment on or prior to Cycle 2 Day 1 for Part 1 subjects and Week 13 Day 1 for Part 2-4 subjects.
  - In the event that this occurs, pharmacodynamic biomarker analyses may be repeated, as a sensitivity analysis, without these subjects or excluding data points after initiation of immunosuppressive agents.

7.3 Study Population

7.3.1 Subject Disposition

Summary:

- Screening period: The number (%) of subjects of the following will be summarized on the population of All Enrolled Subjects.
  - All enrolled into the study
  - Entering the treatment period
  - Enrolled but not entering the treatment period together with the reasons
- End of treatment period: The number (%) of subjects of the following will be summarized by part, cohort/arm, and overall, based on the population of All Treated Subjects.
  - All treated subjects
  - Subjects continuing in the treatment period
  - Subjects not continuing in the treatment phase together with the reasons
  - Subjects continuing in the study
- End of follow-up period: The number (%) of subjects of the following will be summarized by part, cohort/arm, and overall, based on the population of All Treated Subjects.
  - All treated subjects
  - Subjects continuing to be followed
  - Subjects not continuing to be followed together with the reasons
- End of survival follow-up period: The number (%) of subjects of the following will be summarized by part, cohort/arm, and overall, based on the population of All Treated Subjects.
  - All treated subjects
  - Subjects continuing to be followed

- Subjects not continuing to be followed together with the reasons

Listing:

- Screen failures: Subjects who discontinued from the study pre-treatment for screen failures will be listed with the reason for screen failure
- Subject status at:
  - End of treatment period
  - End of follow-up period
  - End of survival follow-up period
  - End of extension period

7.3.2 Demographic and Baseline Characteristics

The definition of baseline described in Section 6.1.1 will be applied here.

Summary:

The following demographic and baseline characteristics of all treated subjects will be summarized by part, cohort/arm, and overall.

- Age (in years); age category (<65, ≥65)
- Gender
- Race
- Ethnicity (for US only)
- Height
- Baseline Weight
- Baseline Body Mass Index (BMI)
- Baseline ECOG performance status
- Disease characteristics
  - Disease diagnosis, including initial stage/M status and stage/M status at study entry)
  - Subtype of disease
  - Baseline LDH (> ULN vs. ≤ ULN)
  - BRAF mutation status

Listing:

- All relevant data, generally variables listed above
- General medical history
- Tobacco use
- Potential risk factors for pulmonary related events
- Chest X-ray
- Clinical complaints

7.4 Extent of Exposure

The extent of exposure will be characterized according to the number of subjects exposed, the duration of exposure, and the dose to which they were exposed. Analyses in this section will be performed on the population of All Treated Subjects "as treated" as described in Section 6.2.

7.4.1 Study Therapy

The following calculations will not be performed for the subject enrolled in Arm C prior to the closure of that arm in Amendment 06.

Summary:

Descriptive statistics will be provided by part and cohort/arm for the following.

- Nivolumab
  - Number of doses of nivolumab
  - Duration of therapy (weeks) of nivolumab = last dose date - start dose date + 14)/7, only calculated if:
    - Nivolumab is taken as a monotherapy (Part 1, Arm B, and Arm E)
    - Nivolumab and ipilimumab combination therapy if the last dose is nivolumab monotherapy (ie, after the 4th dose in Arms A and D).
  - Duration of therapy (weeks) of nivolumab = (last dose date - start dose date + 21)/7, only calculated if:
    - Nivolumab and ipilimumab combination therapy if the last dose is a combination therapy (ie, the first 4 doses in Arms A and D).
  - Cumulative dose (mg/kg) of nivolumab = the sum of all actual nivolumab doses that a subject received
    - The actual doses received is documented in mg, so prior to taking the sum, the actual dose needs to be divided by the subject's weight at baseline, unless their weight at the most recent visit differs by 10% or more compared to baseline
  - Relative dose intensity (%) = cumulative dose (mg/kg) / [3 mg/kg*(last dose date - start dose date + 14)/14)]*100, only calculated if nivolumab is taken as a monotherapy (Part 1, Arm B, and Arm E).
    - Categories: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%
  - Relative dose intensity (%) = cumulative dose (mg/kg) / [1 mg/kg*(last dose date - start dose date + 21)/21)]*100, only calculated if nivolumab is taken as a combination therapy (Arms A and D) and subject's last dose is in the combo phase.
    - Categories: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%
  - Relative dose intensity (%) = cumulative dose (mg/kg) / [1 mg/kg*4 cycles + 3 mg/kg*(last dose date - 84 + 14)/14)]*100, only calculated if nivolumab is taken as a combination therapy (Arms A and D) and subject's last dose is in the mono phase.
    - Categories: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%
- Ipilimumab
  - Number of doses of ipilimumab

- Duration of therapy (weeks) of ipilimumab = (last dose date - start dose date + 21)/7.
- Cumulative dose (mg/kg) of ipilimumab = the sum of all actual ipilimumab doses that a subject received
  - The actual doses received is documented in mg, so prior to taking the sum, the actual dose needs to be divided by the subject's weight at baseline, unless their weight at the most recent visit differs by 10% or more compared to baseline
- Relative dose intensity (%) = cumulative dose (mg/kg) / [3 mg/kg*(last dose date - start dose date + 21)/21)]*100
  - Categories: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%

In addition, the following will also be summarized.

- Number (%) of treated subjects exposed for specified periods of time such as less than 12 weeks, 12 weeks to 6 months, 6-12 months, and more than 12 months by part and arm.

Listing:

- Drug administration
- Number of doses, duration of therapy, cumulative dose, dose intensity, and relative dose intensity

7.4.2 Modification of Study Therapy

Summary:

The following will be provided by part and cohort/arm.

- Nivolumab
  - Number (%) of subjects with dose delay, omission and discontinuation along with the reason
  - Infusion interruptions
    - Number (%) of subjects with at least one infusion interruption along with the reason*
    - Duration of interruption*
    - Number of infusion interruptions per subject
    - Number (%) of subjects with at least one IV infusion rate reduction along with the reason*
- Ipilimumab
  - Number (%) of subjects with dose delay, omission and discontinuation along with the reason
  - Infusion interruptions
    - Number (%) of subjects with at least one infusion interruption along with the reason*
    - Duration of interruption*
    - Number of infusion interruptions per subject
    - Number (%) of subjects with at least one IV infusion rate reduction along with the reason*

*More than one reason or one interruption per patient may be counted in these statistics

Listing:

- All relevant information on dose modification listed above

7.4.3 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. Concomitant medications are defined as medications other than study medications which are taken at any time on-treatment, either with a start date on or after the initiation of study therapy, or with a start date prior to initiation of study therapy and continuing during the study therapy. Concomitant immune modulating medications for adverse event management will be summarized and only include those starting in the on-treatment period.

Summary:

The following prior therapy will be summarized by part, cohort/arm, and overall using frequency statistics.

- Prior therapy, including:
  - Prior surgery
  - Prior radiotherapy
  - Prior systemic cancer therapy
    - Setting of regimen
    - Number of prior systemic cancer therapies
    - Systemic cancer therapy category (BRAF inhibitor, Ipilimumab, IL2, etc.)

In addition, the number (%) of treated subjects for the following will also be provided by part, cohort/arm, and overall, medication class, and generic term.

- Non-study medication summary
- Concomitant immune-modulating medications for management of AE by medication class and generic term

Listing:

- All prior and concomitant medications
- Concomitant immune-modulating medications for management of AE by medication class and generic term
- Subsequent therapy (surgery, radiotherapy, systemic cancer therapy) that occurs after first dose of study drug

7.5 Efficacy

Efficacy analyses will be based on the endpoints defined in Section 4.2.2 and performed on All Treated Subjects for the final analysis. Efficacy analyses based on Response Evaluable Subjects may be performed as supportive analyses. If the majority of All Treated Subjects is included in Response Evaluable Subjects, limited efficacy analyses will be performed on the Response Evaluable Subjects (eg, ORR). For interim analyses when the minimum follow-up period is less than sufficient to warrant adequate interpretation of the result, efficacy analyses may be performed on Response Evaluable Subjects.

Time to event distribution (eg, PFS, OS, and DOR) will be estimated using Kaplan-Meier (K-M) method. When appropriate, the median along with 95% CI will be provided using Brookmeyer and Crowley methodology[7] (using log-log transformation for constructing the confidence intervals). Rates at fixed timepoints (eg, PFSR at 6 months or OS at 12 months) will be derived from the K-M estimate and the corresponding CI will be derived based from Greenwood's formula[8]. Confidence intervals for binomial proportions will be derived using the Clopper-Pearson method[9].

Summary:

The following will be summarized by part, cohort/arm, and overall.

- The ORR with corresponding 2-sided 95% CI based on the Clopper-Pearson method, along with each category of BOR.
- The DOR with median (95% CI) and range (min, max) by K-M method. The number of subjects still in response at the time of database lock will be indicated. This summary includes responders (BOR of CR or PR) only.
- The TTR with median (95% CI) and range (min, max) by summary statistics. This summary includes responders (BOR of CR or PR) only
- The PFS and OS with median (95% CI) and range (min, max) by K-M method.
- The PFSR at specified timepoints (eg, Week 24) by K-M method.
- The OSR (eg, Month 12) by K-M method. If the number of subjects at risk is too small (eg, <5 due to high censoring), OSR will not be presented.
  - The currentness of follow-up, defined as the time between last OS contact (ie, last known date alive or death date) and data cut-off date, will be summarized by treatment group. Subjects who died before the 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 based on the actual data and will be described in each deliverable's DPP. An example of the categories are: 0 days, 1-30 days, 31-60 days, 61-90 days, 91-120 days, 120-150 days, 151 or more days.
  - The extent of follow-up defined as the time between first dose date and last known date alive (for subjects who are alive) or death date (for subjects who died) will be summarized descriptively (median, min, max) for all treated subjects.

Figure:

The following will be plotted by part, cohort/arm, and overall.

- Percent change from baseline in target lesion tumor burden over time (ie, spider plot)
- Best percent change from baseline in target lesions (ie, waterfall plot)
- Kaplan-Meier plot of DOR for responders only
- Swimmer plot of TTR, DOR, and time on therapy for responders only
- Kaplan-Meier plot of PFS
- Kaplan-Meier plot of OS

Listing:

The following will be listed by part, cohort/arm, and overall.

- Tumor lesion measurements, including measurements for subjects who received treatment beyond progression
- Tumor evaluation at each visit, including non-target lesions and new lesions, tumor change from smallest sum of diameters in target lesions, and corresponding change (or percent change) from baseline
- Subject level efficacy for All Treated Subjects: BOR, OS, PFS, best response in target lesions, death indicator, duration of response and time to response for responders
- Survival - survival status, first dose date, last dose date, last known alive date, death date, time to death

7.5.1 Other Observations Related to Efficacy

Additional exploratory efficacy analysis may be performed if deemed appropriate by the study team, provided there is sufficient data. These will be detailed in the DPP. Examples include, but are not limited to:

- Efficacy using immune-related response criteria
- Efficacy by clinically meaningful disease characteristics such as prior therapy (eg BRAF inhibitor, IL2, etc), BRAF mutation status, or baseline LDH level

7.6 Safety

Analysis of safety will be based on All Treated Subjects and presented by part, cohort/arm, and overall. Deaths and SAEs will be listed using All Enrolled Subjects. The treatment group will be "as treated" as defined in Section 6.2.

Adverse events will be coded according to the most recent version of MedDRA at the time of each database lock and the severity will be graded using the NCI CTCAE version 4.0. 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.

Listing of AEs will include all enrolled subjects as SAEs and deaths are collected pretreatment. Summaries of AEs will include (1) events occurring from the first dose date to 100 days

(inclusive) after the last dose of study treatment for subjects who are off study treatment and (2) all events occurring from first dose date for subjects who are still on study medication.

All recorded AEs will be listed and tabulated by system organ class (SOC), preferred term (PT), unless otherwise specified. When reporting AEs by CTC grade, summary tables will be provided based on the event with worst CTC grade (independent of relationship to study medication). Subjects will only be counted (1) once at the PT level, (2) once at the SOC level, and (3) once in the 'Total subject' row at their worst CTC grade, regardless of SOC or PT.

The analysis of laboratory results will be based on All Treated Subjects. Laboratory results will be categorized according to NCI CTCAE version 4.0 grade. Baseline is defined in Section 6.1.1. Summaries of laboratory results include baseline and (1) post-baseline results up to 100 days (inclusive) after the last dose of study treatment for subjects who are off study treatment and (2) all available post-baseline results for subjects who are still on study medication.

7.6.1 Deaths

Summary:

Deaths will be summarized by part and cohort/arm.

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

Listing:

- All recorded deaths for All Enrolled Subjects will be listed

7.6.2 Other Serious Adverse Events

Summary:

The following will be summarized by part and cohort/arm.

- 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. This table will be restricted to events with incidence greater or equal to 1% in any treatment group.
- Overall summary of drug-related SAEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.

Listing:

- By-subject SAE listing will be provided for the All Enrolled Subjects.

7.6.3 Adverse Events Leading to Discontinuation of Study Therapy

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

Summary:

The following will be summarized by part, cohort/arm, and overall.

- 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.

Listing:

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

7.6.4 Adverse Events Leading to Dose Modification

Summary:

Adverse events leading to dose delay/reduced/interrupted will be summarized by part, cohort/arm, and overall.

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

Listing:

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

7.6.5 Overall Adverse Events

Summary:

Adverse events and drug-related AEs will be tabulated by descending frequency of SOC and descending frequency of PT within each SOC, unless specified otherwise. The following will be summarized by part, cohort/arm and overall.

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

Listing:

- All recorded AEs occurring in the pretreatment, on-treatment, and post treatment period will be listed.

7.6.6 Select Adverse Events

The select AEs consist of a list of preferred terms grouped by specific categories (endocrine, hypersensitivity/infusion reaction, gastrointestinal, hepatic, pulmonary, renal, skin, and other immune events, including encephalitis). These categories are defined by the Sponsor and may be changed based on new or evolving knowledge. The list that is most current at the time of analysis will be used. The final list used for the CSR will be included in an Appendix of the CSR.

Summary:

The following will be summarized by part, cohort/arm and overall.

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

Listing:

- Select AE definition
- By-subject select AE listing will be provided.

In addition, time to onset of select AE and time to resolution of select AE may be summarized by part, cohort/arm, and overall.

7.6.7 Multiple Events

Analyses that take into account the multiple occurrences of a given AE will be conducted. In order to prepare these analyses, the CRF data will be processed according to standard BMS algorithms[10] in order to collapse AE records into unique records based on the PT. This data will be presented as the rate per 100 patient-years. These analyses will take into account all on-treatment events (allowing more than 1 event per subject) and the total duration of AE follow-up that is based on exposure to the study medication. The patient-years will be computed as the sum over the subjects' follow-up expressed in years and is defined as:

- Date of last dose of study treatment - date of first dose of study treatment + 100 + 1 days, for subject who are off study treatment and were followed for at least 100 days after last dose of study medication.
- Last known date alive - date of first dose of study medication + 1, for subjects who are still on-treatment or who are off study treatment and were followed less than 100 days after last dose of study medication.

Summary:

The following summary tables will be provided:

- Total number and rate (exposure adjusted) of occurrences for all AEs.
- For select AEs:
  - Frequency of unique AEs, meaning the number of subjects experiencing an AE once or multiple times by part, cohort/arm and overall.

Listing:

- Unique instances of all AEs, ie, after duplicates have been eliminated and overlapping and contiguous occurrences of the same event (ie, same PT) have been collapsed.

7.6.8 Clinical Laboratory Evaluations

Clinical laboratory data will be first analyzed using International System of Units (SI). Analyses will be repeated using US conventional units. In addition, further analyses on specific laboratory parameters will be performed as described in Sections 7.6.8.1 and 7.6.8.2. The analysis population for each laboratory test is restricted to treated subjects who underwent that laboratory test.

Summary:

The number (%) of subjects with the following will be summarized by part, cohort/arm, and overall, if appropriate, using the worst CTC grade on-treatment per subject.

- Post-baseline grade
- Shift-table of worst on-study CTC grade compared to baseline CTC grade
- Descriptive statistics of laboratory test result and their changes from baseline by part, cohort/arm, overall, and study day

Listing:

- A by-subject listing of these laboratory parameters will be provided.
- Laboratory abnormality criteria
- Laboratory results outside of normal range

7.6.8.1 Abnormal Hepatic Test

Summary:

The number of subjects with the following laboratory abnormalities from on-treatment evaluations will be summarized by part, cohort/arm, and overall.

- ALT or AST > 3 x 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

Figure:

Scatter plots will be produced for the following hepatic laboratory parameters. On-treatment peak total bilirubin and on-treatment peak AST/ALT may or may not happen on the same day of liver testing.

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

Listing:

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

7.6.8.2 Abnormal Thyroid Test

Summary:

The number of subjects with the following laboratory abnormalities from on-treatment evaluations will be summarized by part, cohort/arm, and overall.

- TSH value > ULN and
  - with baseline TSH value ≤ ULN
  - at least one FT3/FT4 test value < LLN
- TSH < LLN and
  - with baseline TSH value ≥ LLN
  - at least one FT3/FT4 test value > ULN

Listing:

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

7.6.9 Electrocardiograms

Listing:

- A by-subject listing of all ECG measures
- A listing of only abnormal ECG interpretations

7.6.10 Vital Sign and Physical Findings

Summary:

The following parameters and their corresponding change from baseline will be summarized by part, cohort/arm, overall, and timepoint.

- Vital Signs
- Body weight, BMI, and performance status

Listing:

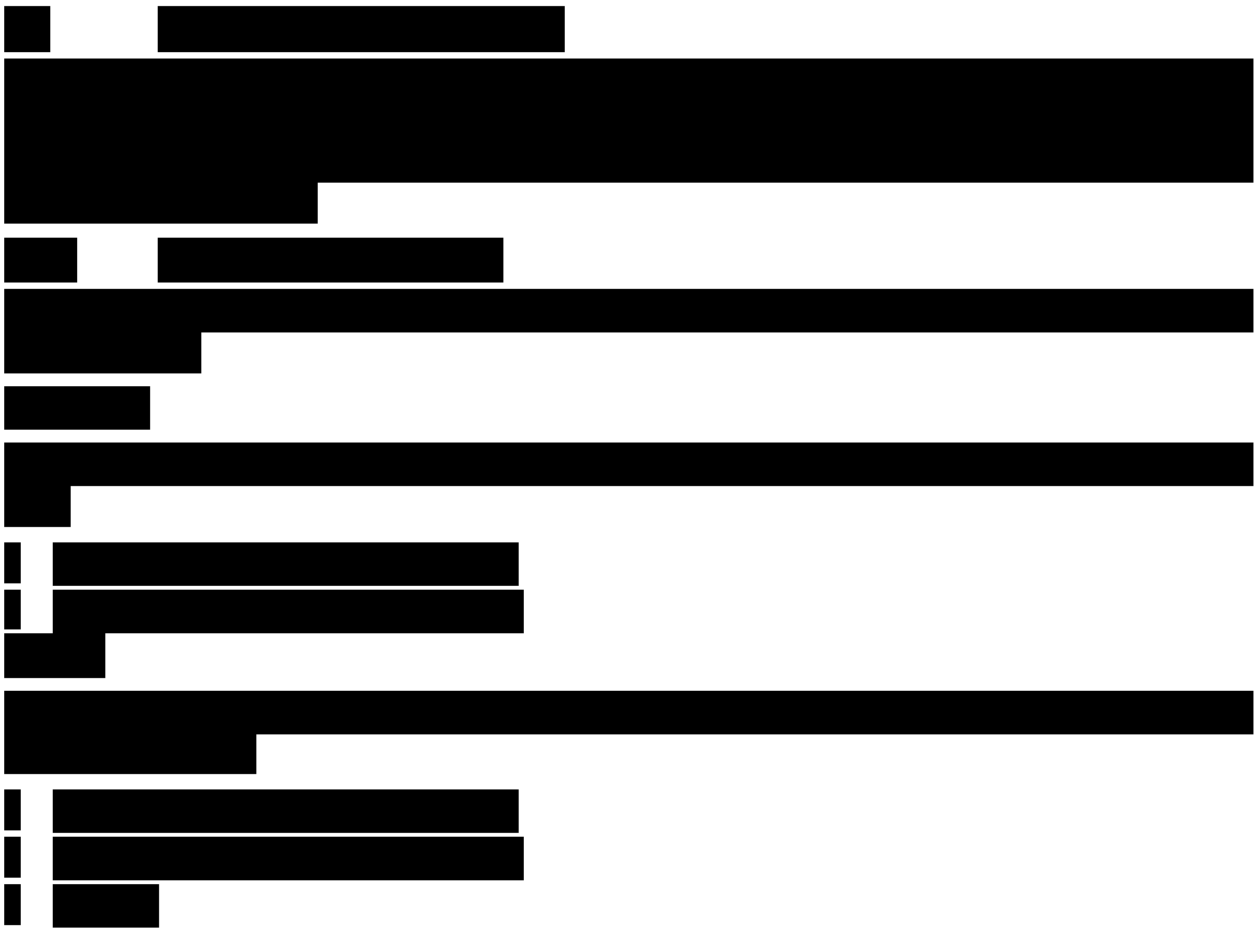
- Vital Signs
- Height, body weight, BMI, and performance status
- Abnormal physical examination findings

7.6.11 Other Observations Related to Safety

Listing:

The following by-subject listings will be produced if data exists.

- Pulse Oximetry
- Diagnostic Procedures
- Medical Treatment Procedures
- Pregnancy Testing
- Clinical Safety Program (CSP) Listing
  - This includes the safety event, potential risk factor, diagnostic procedure, and treatment medications for all CSP categories.



[redacted]

[redacted]

7.8.1 Primary Biomarker Analysis

Summary:

The primary biomarker endpoints described in Table 4.1-1 will be summarized by part, cohort/arm, overall, and by timepoint. The analysis will include descriptive statistics of the parameters and their corresponding change (or percent change) from baseline. This analysis is expected to be included in the CSR. In addition, frequency statistics may be tabulated for biomarkers which have many observations that are <LLOQ or >ULOQ and are not numerically evaluable.

[redacted]

7.8.2 Secondary Biomarker Analysis

To analyze the potential association between PD-L1 expression (by IHC) and clinical efficacy measures, the following definitions will be used:

- PD-L1 expression is defined as the percent of tumor cells demonstrating plasma membrane PD-L1 staining of any intensity in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 IHC assay unless otherwise specified.
- PD-L1 expression value refers to the continuous variable, percent of tumor cells.
- PD-L1 expression level ($\geq$ x%, $<$ x%, Unknown) in this study is defined where x is 1%, 5%, or 10% for quantifiable PD-L1 expression value. PD-L1 level for subjects without PD-L1 assessment will be categorized as 'unknown' status. Additional values for x beyond what is listed may also be explored.
- PD-L1 expression is assessed in archived tumor tissue and freshly collected tumor samples at screening and on treatment. Analysis by pre-treatment status will be conducted in archived,

baseline, and overall. Overall expression level is defined as ≥ x% if any of the archived and/or baseline specimens are ≥ x%.

- Responder is defined as subjects with a BOR of CR or PR. Non-responder is defined as subjects with a BOR not meeting the criteria for CR or PR.
  - For interim analyses, an unconfirmed CR or unconfirmed PR may be used.
  - For the CSR and final analyses, the CR and PR must be confirmed.
- Disease control rate (DCR) is defined as the proportion of subjects with a BOR of CR, PR, or SD.
  - For interim analyses, an unconfirmed CR or unconfirmed PR may be used.
  - For the CSR and final analyses, the CR and PR must be confirmed.

The below analyses is expected to be included in the CSR, but may not be performed depending on availability and interpretability of the data.

Summary:

Summaries will be provided for by part, cohort/arm, and overall (if appropriate) for PD-L1 level at pre-treatment using each sample type (archived, baseline, and overall).

- A frequency distribution of PD-L1 value and/or level
  - For availability of tumor tissue sample and assay result at different times, the number (%) of treated subjects with tumor tissue sample together with non-missing PD-L1 expression value and/or level will be provided.
  - A table will also be created for on-treatment PD-L1 expression value and/or level
- The BOR by PD-L1, which includes ORR by PD-L1 expression level and DCR by PD-L1 expression level
- The DOR and TTR by PD-L1 expression level
- The PFS and OS by PD-L1 expression level
- The PFSR and OSR at specified timepoints by PD-L1 expression level
  - Specified timepoints will be consistent with timepoints used in the efficacy analysis.

[redacted]

  - Not PP - Last Sample Positive
  - Other Positive
- Neutralizing Positive
- ADA-negative

Listing:

- All immunogenicity assessments
- ADA assessments for subjects with neutralizing positive

7.9.1.1 Clinical Implications

Clinical implications of nivolumab immunogenicity will be primarily focused on subjects with persistent ADA-positive relative to ADA-negative. Subjects with any ADA-positive samples after initiation of treatment (relative to baseline) may be used to explore clinical implications.

Effect of immunogenicity on clearance of nivolumab will be explored by comparison of clearance estimates (determined by PPK analysis). Effect of immunogenicity on safety will be explored by examining the frequency and type of AEs of special interest such as hypersensitvity/infusion reaction. Summary tables for incidence of overall and each of the preferred terms will be provided, if the number of subjects is of sufficient size (eg, at least 10 subjects). Otherwise, individual subject's safety profile will be examined and described based on a listing. Clinical implications on efficacy will also be explored similarly. Association between trough concentrations of nivolumab or combination drug (eg, ipilimumab) and ADA assessments may be explored, as needed.

7.9.2 Pharmacogenomics Analyses

The following potential analyses may be performed as appropriate and may not necessarily be included in the CSR.

- Examine demographic factors such as race/ethnicity, age, and gender to determine appropriate stratification or adjustment for the analysis.
- Summarize allele and genotype frequencies from the sample with 95% confidence intervals.
- Explore the relationship among genetic variation, expression of genes and proteins, and clinical outcomes using methods such as, but not limited to, chi-squared tests, linear models, generalized linear models, non-parametric models, survival models, or clustering algorithms.

8 CONVENTIONS

8.1 General Conventions

- In general, BMS Global Standard time windowing, imputation rules, and counting rules will be applied.
- The following conversion factors will be used to convert days to months or years.
  - 1 month = 30.4375 days
  - 1 year = 365.25 days
- Duration (e.g. time-to onset, time-to resolution) 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.
- Safety data will be handled according to the BMS safety data conventions[11]. This document includes descriptions on how to analyze AE data as well as how to handle partial dates, missing dates, and unknown end dates when analyzing safety data.

8.2 Multiple Measurements

Laboratory Measures

For tabulations of changes from baseline the following will be used, in a hierarchical sequence, to select the post-treatment measurement included in the analysis (if a criterion does not apply it would be skipped in the sequence):

- If multiple laboratory measurements are obtained within the same scheduled time frame, then the measurement obtained on the time closest to the target time/day will be used;
- If more than one value meets the above criterion, then the measurement obtained on the earlier time will be used;

For tabulations by CTC grade and summarized by worst toxicity grade, if multiple laboratory measurements are obtained within a analysis period (post-baseline), then the worst measurement within the analysis period, respectively, will be used.

Vital Signs

The following criteria will be used, in a hierarchical sequence, to select the post-treatment measurement included in the analysis:

- If multiple vital sign measurements are obtained within the same scheduled time frame, then the measurement obtained on the time closest to the target time/day will be used;
- If more than one value meets the above criterion, then the measurement obtained on the earlier time will be used;
- If more than one value meets the above criterion, then the average value will be used.

8.3 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[12]
- For missing and partial adverse event resolution dates, imputation will be performed as follows (these conventions may change):
  - If only the day of the month is missing, the last day 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.

- 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[13]

9 CONTENT OF REPORTS

The complete list of analyses contributing to the clinical study report and other interim analyses will be given in the Data Presentation Plan.