Statistical Analysis Plan for

Official Title of Study

A Phase 1b, Open-Label, Multicenter, Multidose, Dose-Escalation Study of MDX-1106 (BMS-936558) in Combination with Ipilimumab (BMS-734016) in Subjects with Unresectable Stage III or Stage IV Malignant Melanoma

NCT01024231

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STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

CA209004 (MDX1106-04): A PHASE 1B, OPEN-LABEL, MULTICENTER, MULTIDOSE, DOSE-ESCALATION STUDY OF MDX-1106 (BMS-936558) IN COMBINATION WITH IPILIMUMAB (BMS-734016) IN SUBJECTS WITH UNRESECTABLE STAGE III OR STAGE IV MALIGNANT MELANOMA

PROTOCOL CA209004

VERSION # 3.0

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2 STUDY DESCRIPTION

2.1 Study Design

This is a Phase 1b, open-label, multi-center, multi-dose, dose-escalation study of nivolumab (BMS-936558, MDX-1106) in combination with ipilimumab (BMS-734016, MDX-010). Nivolumab and ipilimumab are fully human monoclonal antibodies (mAb) against PD-1 and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), respectively. Study drugs will be administered either concurrently (Cohorts 1 through 5 and Cohort 8) or in a sequenced regimen (Cohorts 6 and 7). Up to approximately 126 subjects with unresectable Stage III or Stage IV melanoma (MEL) will be enrolled in the study.

For subjects enrolled in the concurrent dose cohorts (Cohorts 1 through 5), the study will consist of the following 5 periods: Screening (up to 4 weeks), Induction (up to 24 weeks), Maintenance (up to 96 weeks), Follow-up (minimum of 12 weeks), and Survival Follow up (up to 3 years).

For subjects enrolled in the sequenced regimen cohorts (Cohorts 6 and 7), the study will consist of the following 4 periods: Screening (up to 4 weeks), Study Treatment (up to 96 weeks), Follow-up (minimum of 12 weeks), and Survival Follow up (up to 3 years)

For subjects enrolled in Cohort 8, the study will consist of the Combination Period (12 weeks), Monotherapy Period (96 weeks), Follow-up (minimum of 12 weeks), and Survival Follow up (up to 3 years).

The dose-limiting toxicity (DLT) evaluation interval is defined as up to 63 days after the first dose of either study drug or until 21 days after the third dose of both study drugs, whichever is longer. Subjects who withdraw from the study during the DLT evaluation interval for reasons other than a DLT will be replaced.

An independent Early Development Advisory Committee (EDAC) consisting of 3 oncology experts who have substantial experience in the use of ipilimumab in MEL will review the adverse event data on an ongoing basis for safety and recommend whether:

- an adverse event meets the criteria for a dose-limiting toxicity (DLT),
- to hold dosing and/or enrollment pending review and outcome of suspected DLTs,
- to continue dosing, dose-escalation, dose de-escalation, and/or cohort expansion, or
- to end dosing and/or enrollment.

If MTD is exceeded, an alternate dose escalation schema may be explored in consultation and agreement between the investigators, Sponsor and EDAC. For example, when Cohort 3 exceeded MTD, Cohort 2a of 3mg/kg of nivolumab + 1mg/kg of ipilimumab was used.

No subject will be permitted individual dose escalations.

2.2 Treatment Assignment

Table 1: Treatment Assignment

Cohort	Dose	Assignment Method	Sample Size	Notes
1	8 doses of 0.3 mg/kg of nivolumab Q3W + 4 doses of 3 mg/kg of ipilimumab Q3W in Induction Period and 8 doses of both study drugs Q12W in Maintenance Period	open label	N=14	Implemented in the study
2	8 doses of 1 mg/kg of nivolumab Q3W + 4 doses of 3 mg/kg of ipilimumab Q3W in Induction Period and 8 doses of both study drugs Q12W in Maintenance Period	open label	N=17	Implemented in the study
2a	8 doses of 3 mg/kg of nivolumab Q3W + 4 doses of 1 mg/kg of ipilimumab Q3W in Induction Period and 8 doses of both study drugs Q12W in Maintenance Period	open label	N=16	Added dose cohort after MTD was reached per protocol specification
3	8 doses of 3 mg/kg of nivolumab Q3W + 4 doses of 3 mg/kg of ipilimumab Q3W in Induction Period and 8 doses of both study drugs Q12W in Maintenance Period	open label	N=6	Dose that exceeded MTD due to DLT
4	8 doses of 10 mg/kg of nivolumab Q3W + 4 doses of 3 mg/kg of ipilimumab Q3W in Induction Period and 8 doses of both study drugs Q12W in Maintenance Period	open label	N=0	Dose cohort not implemented because MTD has been reached

Table 1: Treatment Assignment

Cohort	Dose	Assignment Method	Sample Size	Notes
5	8 doses of 10 mg/kg of nivolumab Q3W+ 4 doses of 10 mg/kg of ipilimumab Q3W in Induction Period and 8 doses of both study drugs Q12W in Maintenance Period	open label	N=0	Dose cohort not implemented because MTD has been reached
6	1mg/kg of nivolumab Q2W for 12 treatment cycles (48 doses) following ipilimumab monotherapy administered prior to enrollment on this study	open label	N=17	Implemented in the study
7	3 mg/kg of nivolumab Q2W for 12 treatment cycles (48 doses) following ipilimumab monotherapy administered prior to enrollment on this study	open label	N=16	Implemented in the study
8	4 doses of 1 mg/kg of nivolumab Q3W + 4 doses of 3 mg/kg of ipilimumab Q3W in Combination Period and 48 doses of nivolumab Q2W	Open label	N= up to 40 planned	Implemented in the study

MTD = maximum tolerated dose; nivolumab = BMS-936558 / MDX-1106; Q2W = every two weeks; Q3W = every 3 weeks; Q12W = every 12 weeks.

2.3 Blinding and Unblinding

This is an open-label study. Blinding and unblinding is not applicable in this study.

2.4 Protocol Amendments

The protocol has 6 amendments. The table below summarizes the main purpose of each amendment (Please refer to Document History of the most recent protocol for further details).

Amendment No.	Amendment Date	Main Purpose of Amendment
Amendment 01	14-Oct-2009	The changes made in Revised Protocol 01/Amendment 1 consist primarily of safety changes requested by the Food and Drug Administration (FDA) and administrative/procedural changes due to the acquisition of Medarex, Inc. by Bristol-Myers Squibb
Amendment 02	15-Dec-2009	Changes included a requirement during the dose escalation phase to not dose the next subject until the previous subject's Day 8 safety labs have been reviewed; the change in sponsor contact information; changes to the pharmacokinetic sample collection schedule; clarifications to inclusion criteria 6, 7, and 11; clarifications to exclusion criteria 6, 7, 9, and 10; and changes to pharmacodynamic testing schedule
Amendment 03	01-Oct-2010	Changes included revisions to dose levels of nivolumab and ipilimumab used in Cohorts 2 and 3; allowed for expansion to n=12 for any cohort to gain additional safety experience; updated safety experience for the combination; and included clarifying language on safety and statistical sections.
Amendment	16-May-2011	Changes include adjustments to the definition of DLT; and changes to the inclusion/exclusion criteria to exclude subjects on prior pivotal phase 3

Amendment No.	Amendment Date	Main Purpose of Amendment
04		ipilimumab studies with overall survival as the primary endpoint.
Amendment 05	06-Feb-2012	Changes include addition of cohorts 6 and 7, and inclusion of revised eligibility and time and events tables for these cohorts. These cohorts will evaluate nivolumab as monotherapy for subjects that received recent prior ipilimumab within prior 4-12 weeks prior to start study therapy. Also added is language surrounding retreatment (reinduction) of ipilimumab therapy for those who have progressed after deriving clinical benefit in the setting of maintenance or follow-up phases in the study.
Amendment 06	10-Apr-2013	Enrollment of up to 40 additional subjects in cohort 8 proposed under this amendment will further extend the clinical experience with concurrent therapy and support dose selection for future clinical studies. Language also has been included to indicate which dose groups were not utilized due to protocol mandated MTD determination and to update total number of subjects. Updated safety information has been added. New contraceptive guidance is included for nivolumab due to new preliminary reproductive toxicology data. Clarifications have been incorporated and typographical errors have been corrected.

3 OBJECTIVES

3.1 Primary

The primary objective of this study is to assess the safety and tolerability of treatment with nivolumab (BMS-936558, MDX-1106) in combination with ipilimumab (BMS-734016) when administered concurrently or as sequenced regimens in subjects with unresectable Stage III or Stage IV malignant melanoma (MEL).

3.2 Secondary

The secondary objectives of this study are to:

- assess the preliminary efficacy of nivolumab (BMS-936558, MDX-1106) in combination with ipilimumab (the study drugs) when administered concurrently or as sequenced regimens;
- assess safety, tolerability and preliminary efficacy of the concurrent regimen at the proposed Phase 3 dose and schedule of the combination
- assess the host immune response (immunogenicity) to each study drug; and
- assess the multidose pharmacokinetic peak and trough concentration profiles of each study drug when given in combination using distinct regimens.

[redacted]

- [redacted]

4 ENDPOINTS

4.1 Primary endpoints

Primary safety and tolerability endpoints include: incidence of all cause and treatment related adverse events (AE) and serious AEs (SAE), select AE, death, AEs that led to discontinuation, and lab abnormalities.

4.2 Secondary endpoints

4.2.1 Efficacy endpoints

The following set of efficacy variables are defined by immune-related Response Criteria (irRC) that were developed from standard mWHO response criteria. It is the basis for efficacy evaluation and treatment decisions as applied in the protocol.

- **Best Overall Response Using irRC (irBOR)**: irBOR is the best immune-related response designation over the study as a whole, based on tumor assessment per immune-related response criteria as specified in the Protocol Appendix 3, recorded between the dates of first dose until the last available tumor assessment for the individual subject in the study.
- **Aggregate Clinical Activity Rate (ACAR)**: Total number of subjects whose best overall response using irRC (irBOR) is immune-related complete response (irCR), immune-related partial response (irPR), CR, PR, unconfirmed CR or PR, SD≥24 weeks or irSD≥24 weeks divided by the total number of subjects in the population of interest.

4.2.2 Immunogenicity

Please note that "human anti-human antibodies (HAHA)" as used in the protocol is no longer used for immunogenicity and will be replaced by anti-drug antibody (ADA).

Endpoints for the study are incidence rates of persistent positive ADA as well as neutralizing positive ADA from initiation of study medication and up to and including 100 days of the last study medication dosing. ADA for both nivolumab and ipilimumab will be assayed from immunogenicity samples.

Based on recommendation from BMS Immunogenicity Council, Harmonization of Clinical Immunogenicity Reporting by an Initiative of the Therapeutic Protein Immunogenicity Focus Group of the American Association Pharmaceutical Scientists[2], and the FDA Guidance for Industry Immunogenicity Assessment for Therapeutic Protein Products[3], the following definitions will be applied:

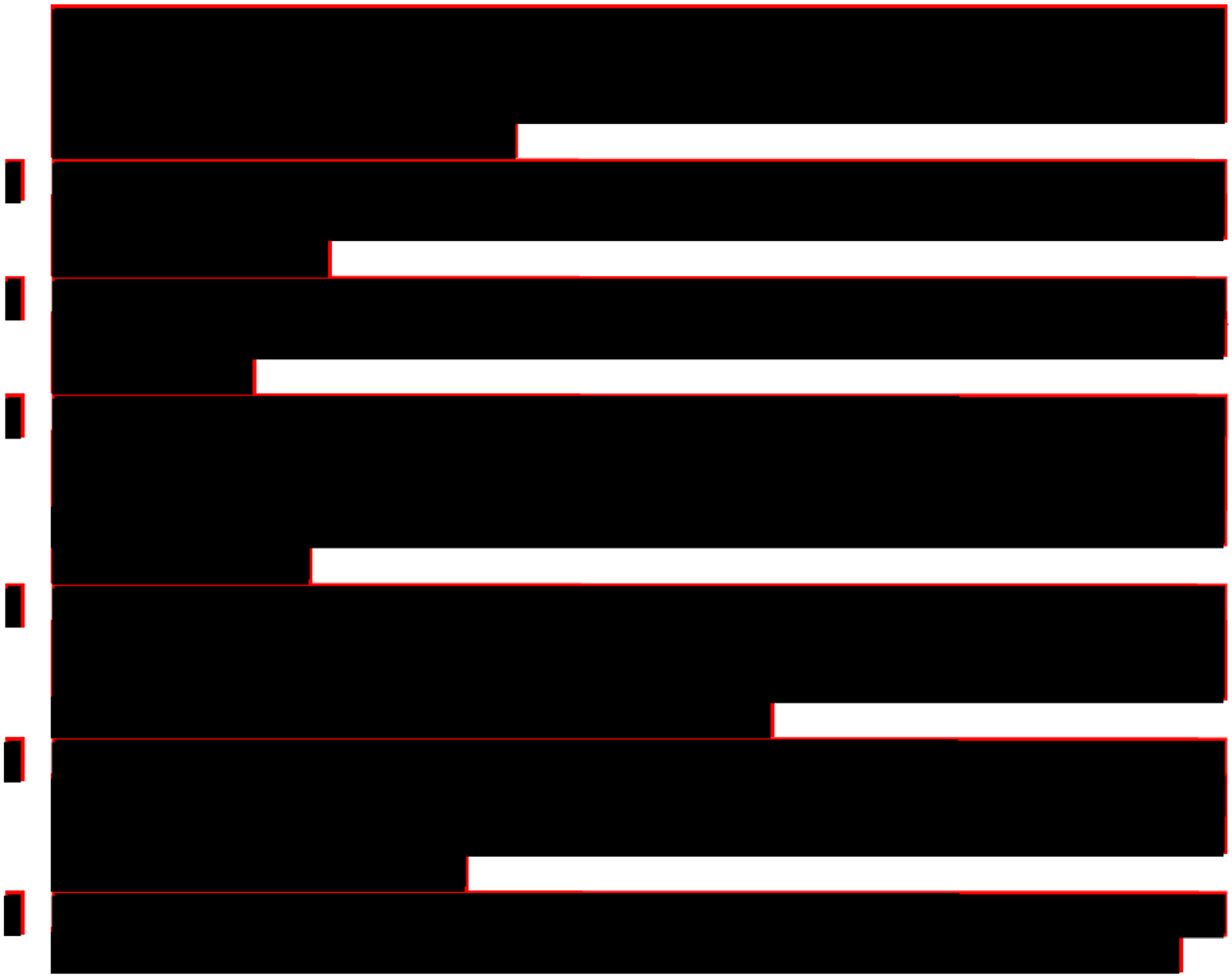
ADA Status of a Sample:

- Baseline ADA Positive Sample: ADA is detected in the last sample before initiation of treatment
- ADA Positive Sample: After initiation of treatment, (1) an ADA positive sample in a subject who is baseline ADA negative, or (2) an ADA positive sample with ADA titer to be at least 4-fold or greater (≥) than baseline positive titer
- ADA Negative Sample: After initiation of treatment, ADA not positive sample relative to baseline

ADA Status of a Subject:

- Baseline ADA Positive Subject: A subject with baseline ADA positive sample
- ADA Positive Subject: A subject with at least one ADA positive sample relative to baseline at any time after initiation of treatment during the defined observation time period
  1) *Persistent Positive:* ADA positive sample at 2 or more sequential time points, where the first and last ADA positive samples at least 8 weeks apart.
  2) *Only the Last Sample Positive:* Not persistent but ADA positive sample in the last sampling time point.
  3) *Other Positive:* Not persistent but some ADA positive samples with the last sample being negative
  4) *Neutralizing Positive:* At least one ADA positive sample with neutralizing antibodies detected.
- ADA Negative Subject**:** A subject with no ADA positive sample after the initiation of treatment

[redacted]



5 SAMPLE SIZE AND POWER

A total of up to approximately 126 subjects are to be enrolled in this study based on the study design for dose escalation and safety evaluation requirements. The sample size cannot be precisely determined because it depends on the observed toxicity.

If among 12 subjects at each dose there are 1 (8.3%), 2 (17%), or 3 (25%) events of interest observed, then the 70% confidence interval for this event rate would be (1.4% to 25%), (5.8% to 35%), or (11.4% to 44%) respectively. There is 85% confidence that the event rate observed in similar future trials would not be higher than 25%, 35%, or 44%, respectively.

In addition, if 16 subjects are treated at a dose level, the 70% confidence interval for a tumor response rate would be (4.3% to 27%) if 2 (12.5%) subjects had a tumor response, and it would be (8.5% to 34%) if 3 (19%) subjects had a tumor response.

Based on the actual sample size treated at the time of amendment #6, and 40 subjects planned in cohort 8, a total of up to 126 subjects may be treated in this study.

Clinical experience to-date demonstrates that an objective response rate of approximately 50% with concurrent dose regimen. Furthermore, approximately 30% of subjects treated with the

concurrent regimen experience a >80% reduction in target disease burden by week 12. Under this amendment (amendment #6), if objective responses are observed in 20 of 40 subjects enrolled in Cohort 8 (i.e. the observed response rate is 50%), then the lower bound of the 90% confidence interval for the true response rate with this combination dose will exclude a 35% response rate. Similarly, if >80% reduction in target disease burden is observed in 16 of 40 subjects (40% of subjects), then the lower bound of the 90% confidence interval for the true incidence will exclude a 30% rate.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

Screening Period (All Cohorts): The Screening Period is defined as the 28 days following initiation of screening assessments and before administration of the first dose of any study drug, during which subjects are evaluated for study eligibility.

Induction Period (Cohort 1 - 5): The Induction Period consists of up to 8 intravenous (i.v.) infusions of nivolumab on Days 1, 22, 43, 64, 85, 106, 127, and 148 and up to 4 i.v. infusions of ipilimumab on Days 1, 22, 43, and 64 with response assessments at Days 85 and 127. Subjects with an overall response of irSD, irPR, immune-related complete response irCR, or unconfirmed irPD at the end of the Induction Period will enter the Maintenance Period. Subjects with confirmed irPD during the Induction Period will discontinue the study drugs, complete Follow-up Visits 1 and 2, and then enter the Survival Follow-up Period. Subjects without evidence of confirmed progression during the Induction Period with either a poor performance status (ECOG > 2) or toxicity requiring discontinuation of the study drugs will enter the Follow-up Period until confirmed irPD, initiation of a new MEL treatment, completion of all Follow-up Visits, or a total duration of 2.5 years since the first dose of any study drug; whichever occurs first. Subjects will then enter the Survival Follow-up Period.

Maintenance Period (Cohorts 1-5): The Maintenance Period consists of up to 8 i.v. infusions of nivolumab and ipilimumab every 12 weeks with response assessments at these same visits. Additional visits for safety evaluation only will be performed every 6 weeks (Weeks 42, 54, 66, 78, 90, and 102) and at Week 30 (this visit will also include a response assessment). The results of the scheduled response assessments must be reviewed to determine and document continued eligibility prior to administration of the study drugs. After completing the Maintenance Period, subjects will complete Follow-up Visits 1 and 2, and then enter the Survival Follow-up Period. Subjects with a confirmed irPD during the Maintenance Period will discontinue the study drugs, complete Follow-up Visits 1 and 2, and then enter the Survival Follow-up Period. Subjects without evidence of confirmed progression during the Maintenance Period with either a poor performance status (ECOG > 2) or toxicity requiring discontinuation of the study drugs will enter the Follow-up Period until confirmed irPD, initiation of a new MEL treatment, completion of all Follow-up Visits, or a total duration of 2.5 years since the first dose of any study drug; whichever occurs first. Subjects will then enter the Survival Follow-up Period.

Cohort 6-7 Dose Administration: Subjects enrolled in Cohorts 6 or 7 will receive nivolumab as monontherapy administered as an i.v., infusion every 2 weeks for up to a maximum of 12 treatment cycles (48 doses). A treatment cycle will consist of 4 doses of nivolumab administered on Days 1, 15, 29, and 43 followed by a tumor assessment on Days 52-56.

Cohort 8 Dose Administration: Subjects will receive 1 mg/kg of nivolumab in combination with 3 mg/kg of ipilimumab every 3 weeks for 4 doses (Combination Period) followed by 3 mg/kg of nivolumab alone every 2 weeks for up to a maximum of 48 doses (16 cycles; Monotherapy Period).

Follow-up Period (All Cohorts): Subjects will complete up to 9 Follow-up Visits for a total duration of 2.5 years since their first dose of any study drug. All subjects will have follow-up visits approximately 6 and 12 weeks after their last dose of the study drugs (Follow-up Visits 1 and 2, respectively). After completing Follow-up Visits 1 and 2, subjects without confirmed irPD who discontinued the study drugs during the Induction or Maintenance Period because of a poor performance status (ECOG > 2) or toxicity will complete up to 7 additional Follow-up Visits (for a total of up to 9 Follow-up Visits) until confirmed irPD, initiation of a new MEL treatment, completion of 9 Follow-up Visits, or a total duration of 2.5 years since the first dose of any study drug; whichever occurs first.

Re-Induction/Re-Initiation Phase: Subjects in Cohorts 1-5 entering the maintenance or follow-up periods with ongoing disease control (ongoing CR, PR, or SD) may be permitted re-induction with the combination of ipilimumab and nivolumab upon confirmed disease progression and after discussion and agreement with the BMS Medical Monitor. Subjects in Cohorts 6-7 entering the follow-up period with ongoing disease control (ongoing CR, PR, or SD) may be permitted re-initiation of study therapy with nivolumab upon confirmed disease progression and after discussion and agreement with the BMS Medical Monitor. Subjects in Cohort 8 will not be permitted re-induction.

Survival Follow-up Period (All Cohorts): All subjects will be followed for survival (via telephone contact every 12 weeks) for up to 3 years.**Treatment Regimens**

Cohort 4 and 5 are not in the table as originally planned because maximum tolerated dose has been reached at Cohort 3.

Cohort	Dose
1	0.3 mg/kg of nivolumab Q3 wks for induction period and Q12 wks for maintenance period + 3 mg/kg of ipilimumab Q3 wks for induction period and Q12 wks for maintenance period
2	1 mg/kg of nivolumab Q3 wks for induction period and Q12 wks for maintenance period + 3 mg/kg of ipilimumab Q3 wks for induction period and Q12 wks for maintenance period
2a	3 mg/kg of nivolumab Q3 wks for induction period and Q12 wks for maintenance period + 1 mg/kg of ipilimumab Q3 wks for induction period and Q12 wks for maintenance period
3	3 mg/kg of nivolumab Q3 wks for induction period and Q12 wks for maintenance period + 3 mg/kg of ipilimumab Q3 wks for induction period and Q12 wks for maintenance period

6	1mg/kg of nivolumab Q2 weeks following Ipilimumab monotherapy administered prior to enrollment on this study
7	3 mg/kg of nivolumab Q2 weeks following Ipilimumab monotherapy administered prior to enrollment on this study
8	1 mg/kg of nivolumab Q3 wks for combination period and Q2 wks for monotherapy period + 3 mg/kg of ipilimumab Q3 wks for combination period.

6.3 Populations for Analyses

- **All Enrolled Subjects**: All subjects who signed the Informed Consent Form.
- **All Treated Subjects**: All subjects who received at least one dose of study medication (either nivolumab or ipilimumab).
- **Response evaluable population**: Response evaluable population will be defined as all subjects who received at least one dose of nivolumab or ipilimumab, have measurable disease at baseline, and one of the following: 1) at least one on-treatment tumor evaluation, 2) clinical progression, or 3) death.
- **PK Population**: All subjects who received nivolumab or ipilimumab and have available concentration-time data.
- **Biomarker Population**: All subjects who received nivolumab or ipilimumab and have available biomarker data.
- **Immunogenicity Population**: All treated subjects with baseline and at least one post-baseline immunogenicity assessment.

7 STATISTICAL ANALYSES

7.1 General Methods

All statistical tabulations and analyses will be done using the Statistical Analysis System (SAS®), version 8.2 or later. Some graphical displays may be generated using S-Plus.

Continuous variables will be summarized using descriptive statistics, i.e. medians, minimums, maximums, and means with standard deviations/standard errors of the mean. Categorical variables will be summarized by frequencies and percentages. Percentages will be rounded and may not always add up to 100.

Some changes were made in the SAP that are different from the protocol, in general for reasons arising from regulatory interactions, changes in treatment practices and opinions in the rapidly evolving immuno-oncology field, and program development needs. Important changes include:

- For adverse event summaries, adverse events on-treatment up to and including 100 days, rather than the protocol specified 84 days, after the last dose of any study medication will be included. This is changed per needs to align between various studies of the nivolumab program to present a consistent set of AE tables and also from regulatory feedback.
- Use of the program-wide standard terminology “Select Adverse Events” in replacement of Adverse Events of Special Interest (EOSI).

7.2 Study Conduct

Programmable deviations from inclusion and exclusion criteria based on the locked database will be listed. Subjects accrued will be listed and summarized by country (all in US) and sites.

7.3 Study Population

7.3.1 Subject Disposition

The number of subjects enrolled into the study, the number of subjects entering the treatment period and the number of subjects enrolled but not dosed (together with the reasons for not being dosed) will be summarized.

The number of treated subjects, number of subjects completing the study and not completing the study (together with the reasons for not completing the study) will be summarized. For each treatment period, number of subjects completing the period and not completing the period (together with the reasons for not completing the period), and subjects still continuing and not continuing in the period will be summarized.

7.3.2 Demographics and Other Baseline Characteristics

Subject demographic and baseline characteristics, including age, sex, race, ethnicity, height, weight, ECOG performance status, and any other study-appropriate data, such as initial and current disease diagnosis at study entry will be presented as by-subject listings and summarized by dose cohort and overall using descriptive statistics.

Disease diagnosis, prior radiotherapy, surgery related to cancer and systemic cancer therapy will be listed and summarized. The numbers and types of prior systemic therapies including immunotherapy, BRAF inhibitor therapy will be summarized and listed.

The status of prior ipilimumab-treated subjects at enrollment (partial response, stable disease, radiographic progression clinically stable) will be summarized for Cohorts 6 and 7.

BRAF mutation status and baseline disease site will be listed and summarized.

7.4 Extent of Exposure

Extent of exposure will be calculated for nivolumab for Cohort 1-8 and ipilimumab for Cohort 1-5 and Cohort 8 respectively.

The duration of a cycle (in weeks) is defined as: (Start date of next cycle - Start of current cycle)/7. The duration of the last treatment cycle is calculated as follows:

- Cohort 1-5: 3 weeks if the last dose is in induction period; or 12 weeks if the last dose is in maintenance period.
- Cohort 6-7: 2 weeks.
- Cohort 8: 3 weeks if the last dose is in combination period; or 2 weeks if the last dose is in monotherapy period.

Duration of therapy (in weeks) is defined as: (last dose date - first dose date)/7 + duration of the last treatment cycle as calculated above.

Delivered dose in mg is provided per CRF form.

Delivered dose (mg/kg) of each cycle is calculated by dividing delivered dose (mg) by body weight (kg), if body weight at time of dosing is not available, previous assessment will be used.

Cumulative dose in mg/kg is defined as: Sum over the duration of the study of all delivered doses (mg/kg) per subject.

Dose intensity of a cycle (in mg/kg) is calculated as the delivered dose in mg/kg divided by the duration of the cycle (in weeks) and multiplied by X, where X =:

- Cohort 1-5: 3 weeks if the last dose is in induction period; or 12 weeks if the last dose is in maintenance period.
- Cohort 6-7: 2 weeks
- Cohort 8: 3 weeks if the last dose is in combination period; or 2 weeks if the last dose is in monotherapy period.

Dose intensity (in mg/kg) is defined as the average of dose intensity (sum over the duration of the study of all dose intensity of each cycle, divided by the number of cycles).

Relative dose intensity (for cohort 1 to 7) is defined as dose intensity divided by planned dose (relative dose intensity = dose intensity / planed dose).

Relative dose intensity (for cohort 8) needs to be calculated differently as the dose for nivolumab changed from 1mg/kg to 3mg/kg from combination period to monotherapy period. A Relative Cycle Intensity has to be calculated first as follows before relative dose intensity can be calculated.

Relative Cycle Intensity (only for cohort 8) is calculated as dose intensity of a cycle divided by planned dose (note that planned dose of nivolumab is 1mg/kg for combination period and 3mg/kg for monotherapy period; and planned dose of ipilimumab is 3mg/kg for combination period and no ipilimumab dosing for monotherapy period).

Relative Dose Intensity (for cohort 8) is defined as the sum of all Relative Cycle Intensities, divided by the number of cycles.

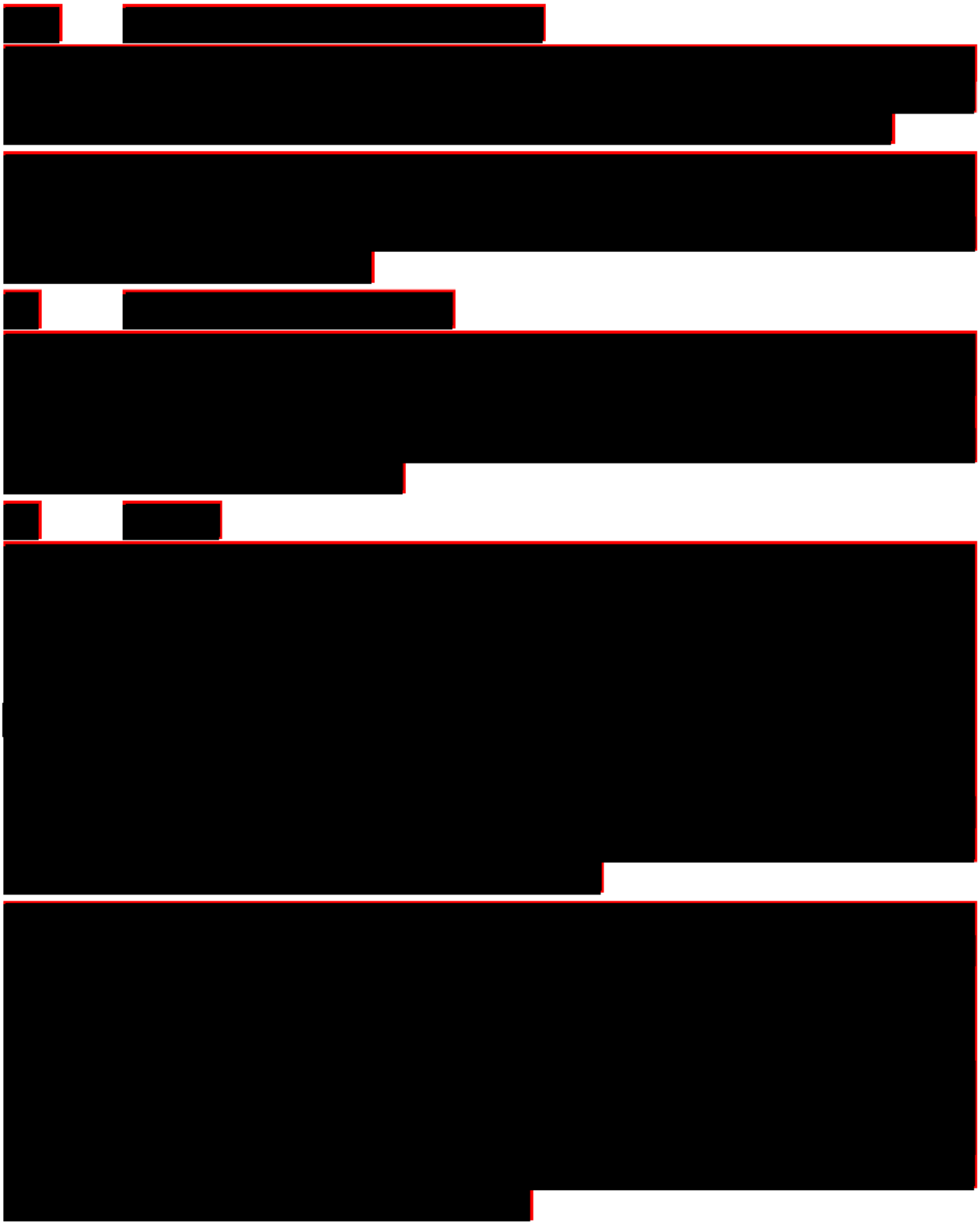
The following parameters will be summarized by dose cohort for all treated subjects:

- Duration of therapy (in weeks)
- Cumulative Dose
- Dose intensity
- Relative dose intensity
- Number of concomitant doses received, as well as number of nivolumab and ipilimumab doses received.

A listing of study drug exposure will be provided. A listing of study medication by batch (or vial) number will be provided.

7.4.1 Dose Changes/Modifications

Dose change (interruption or delay) and the reason will be listed for each subject and summarized.



7.7 Safety

In addition to primary safety endpoints, other safety measurements in the study include the following:

- ECOG
- Vital Sign Measures
- ECG measures, including heart rate, PR, QRS, QT and QTc
- Physical examinations
- Clinical laboratory test results (including hematology, chemistry and liver functions, Rheumatoid Factor, Adrenocorticotropic hormone, Thyroid Stimulating Hormone, C-Reactive Protein, Free T4 level) and abnormalities

Please note that "as treatment emergent adverse event (TEAE)" as used in the protocol is no longer used as a standard Bristol Myers Squibb terminology, the SAP will simply use adverse events (AE) in its place, which means AEs reported with onset dates after start of treatment and up to 100 days after end of treatment.

Analysis of safety will be based on all treated subjects and presented by dose cohort and by total. Listing of adverse events will include all enrolled subjects as SAEs and deaths are collected pretreatment.

Where a subject has the same adverse event, based on preferred terminology, reported multiple times, the subject will only be counted once at the preferred terminology level in adverse event summary tables. Where a subject has multiple adverse events within the same system organ class, the subject will only be counted once at the system organ class level in adverse event summary tables. When reporting adverse events by CTC grade, summary tables will be provided

based on the event with worst CTC grade. Subjects will only be counted once in the "Total subject" row at their worst CTC grade, regardless of SOC or PT.

7.7.1 Death

Deaths will be summarized by dose cohort:

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

By-subject listing of deaths will be provided for the all enrolled subjects population.

7.7.2 Serious Adverse Events

Serious adverse events will be summarized by dose cohort:

- 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.

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

7.7.3 Adverse Events Leading to Discontinuation of Study Therapy

AEs leading to discontinuation will be summarized by dose cohort:

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

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

7.7.4 Adverse Events Leading to Dose Modification

AEs leading to dose reduced/interruption will be summarized for each treatment group:

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

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

7.7.5 Adverse Events

Adverse events will be summarized by dose cohort:

- 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. This table will be restricted to events with an incidence greater or equal to 5% in any treatment group.
- 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 group.

By-subject AE listing will be provided.

7.7.6 Select Adverse Events

Select AEs consist of a list of preferred terms grouped by specific category (e.g. pulmonary events, gastrointestinal events categories). Adverse events which may differ from or be more severe than AEs caused by non-immunotherapies and AEs whose early recognition and management may mitigate severe toxicity are included as select AEs. These categories are defined by the Sponsor and the list that is most current at the time of analysis will be used. Changes may be made to this list with each new version of MedDRA. These AEs are described in the protocol and various other places as immune-related AE (irAE), adverse events of special interest (AEOSI), or inflammatory events regardless of causality (IERC), based on early thinking around the type of these AEs, as those which may be triggered by a loss of tolerance to enteric or self antigens. Although specified in the protocol, moving forward nivolumab as a program is not using the nomenclature of irAE, IERC, or the term "Adverse events of special interest (AEOSI)" which were used for such events in some interim reporting, and the term "select Adverse Events", "select AEs" will be used instead.

Select AEs will be summarized by dose cohort for each category:

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

By-subject select AE listing will be provided.

7.7.7 Immune modulating medication

The percentage of subjects who received immune modulating concomitant medication for management of adverse event and the total medication treatment duration will be reported for each treatment group (percentages of treated subjects by medication class and generic term).

By-subject listing of immune modulating concomitant medications received for AE management will be provided.

7.7.8 Multiple Events

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

- Date of last dose of study treatment - date of first dose of study treatment + 100+1 das, for subject who are off study treatment and were followed 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.

The following summary tables will be provided:

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

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

7.7.9 Vital Signs

Observed vital signs at each time point and the change in vital signs from baseline to each post-baseline measurement (after the first study drug administration) will be summarized by dose cohort using descriptive statistics. This will include temperature, pulse, and systolic and diastolic blood pressures. The percentage of subjects with abnormal changes in vital signs during study drug administration will be summarized by dose cohort.

7.7.10 ECG

For ECG measures, the baseline value is defined as the average of triplicate measure on day 1 pre-dose. Listings of ECG readings and investigator-identified ECG abnormalities will be provided. ECG readings outside pre-specified ranges will be listed and number (%) of subjects with ECG readings outside pre-specified ranges will be tabulated.

7.7.11 Physical Exams

Physical exam abnormal findings will be listed.

7.7.12 Clinical Laboratory Tests

The analysis will be based on all treated subjects with available laboratory test result on-treatment and up to and including 100 days of the last dose of study medication. The number (%) of subjects with the following will be summarized by dose cohort and overall, if appropriate, using the worst CTC grade on-treatment per subject.

- Post-baseline grade
- Grade change from baseline
- Descriptive statistics of laboratory test result and their changes from baseline by dose cohort and study day.

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

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 by dose cohort:

Abnormal Hepatic Function Test

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

- 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

The following scatter plots will be produced for the following hepatic laboratory parameters:

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

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

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

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

Abnormal Thyroid Function Test

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

- TSH value > ULN and
  - with baseline TSH value ULN
  - at least one T3/T4 test value < LLN
- TSH < LLN and
  - with baseline TSH value LLN
  - at least one T3/T4 test value > ULN

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

7.7.13 Performance status

Performance status (ECOG) will be summarized by dose cohort and cycle.

7.7.14 Immune safety

Number (%) of subjects will be reported for the following anti-drug responses will be reported by dose cohort. Number of subjects with neutralizing positive will be reported for subjects with neutralization assay results available.

- Baseline ADA Positive
- ADA Positive
  - Persistent Positive
  - Only the Last Sample Positive
  - Neutralizing Positive
- ADA Negative

Effect of immunogenicity on safety/efficacy will be explored based on subjects with Persistent Positive ADA vs ADA Negative subjects.

A listing will be provided of all available immunogenicity data with corresponding nivolumab and ipilimumab concentration by dose cohort.

7.7.15 Pregnancy

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

7.7.16 Clinical Safety Program (CSP)

Listings by subject will be produced with data from adverse events CSP CRF pages, such as AEs, risk factors, diagnostic procedures, treatment medications for related events.

[redacted]

[redacted]

8 CONVENTIONS

8.1 Safety Data Conventions

Safety data will be handled according to the BMS safety data conventions (described in "Analysis of Safety Data - Reference to CT SOP 109"). 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 Other Conventions

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.

[redacted]