Statistical Analysis Plan for

Official Title of Study

AN OPEN-LABEL, MULTICENTER CLINICAL TRIAL WITH NIVOLUMAB (BMS-936558) MONOTHERAPY IN SUBJECTS WITH ADVANCED OR METASTATIC SQUAMOUS CELL (SQ) NON-SMALL CELL LUNG CANCER (NSCLC) WHO HAVE RECEIVED AT LEAST ONE PRIOR SYSTEMIC REGIMEN FOR THE TREATMENT OF STAGE IIIB/IV SQNSCLC

NCT02409368

29-November-2018

STATISTICAL ANALYSIS PLAN

FOR CLINICAL STUDY REPORT

AN OPEN-LABEL, MULTICENTER CLINICAL TRIAL WITH NIVOLUMAB (BMS-936558) MONOTHERAPY IN SUBJECTS WITH ADVANCED OR METASTATIC SQUAMOUS CELL (SQ) NON-SMALL CELL LUNG CANCER (NSCLC) WHO HAVE RECEIVED AT LEAST ONE PRIOR SYSTEMIC REGIMEN FOR THE TREATMENT OF STAGE IIIB/IV SQNSCLC

CheckMate 171: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 171

VERSION # 2.0

TABLE OF CONTENTS

TABLE 1: ABBREVIATIONS

AE	Adverse event
AEOSI	Adverse events of special interest
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil count
AST	Aspartate Aminotransferase
BMS	Bristol-Myers Squibb
BOR	Best overall response
BP	Blood pressure
BUN	Blood urea nitrogen
CBC	Complete blood count
CR	Complete response
CrCl	Creatinine Clearance
CT	Computed tomography
CTCAE	Common Terminology Criteria for AEs
CRF	Case Report Form, paper or electronic
DILI	Drug-induced liver injury
EAP	Expanded access program
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EGFR-TKI	Epidermal growth factor receptor-tyrosine kinase inhibitor
GCP	Good Clinical Practice
GI	Gastrointestinal
HIV	Human immunodeficiency virus
HRT	Hormone replacement therapy
ICH	International Conference on Harmonization
IVRS	Interactive voice response system
KM	Kaplan Meier
LCSS	Lung Cancer Symptom Score
LDH	Lactate dehydrogenase
LFT	Liver function test
LLN	Lower limit of normal
mPFS	Median progression-free survival
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
O2	Oxygen
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed cell death – 1

PR	Partial response
PFS	Progression-free survival
PRO	Patient-reported outcomes
PS	Performance status
QoL	Quality of life
PT	Preferred terms
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RR	Respiratory rate
SAE	Serious adverse event
SLAE	Select adverse event
SSC	Scientific Steering Committee
SqNSCLC	Squamous cell non-small cell lung cancer
TFT	Thyroid function test
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
WBC	White blood cell

[redacted]

2 STUDY DESCRIPTION

2.1 Study Design

This is an Open-Label, Multicenter Study. The study will include subjects with histologically- or cytologically-documented SqNSCLC who have progressed during or after a minimum of 1 prior platinum doublet-based chemotherapy regimen for advanced or metastatic disease. Subjects will be treated with 3 mg/kg of nivolumab IV every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of consent. Subjects will undergo screening evaluations to determine eligibility within 28 days prior to first dose following signed informed consent. Each 14-day dosing period will constitute a cycle.

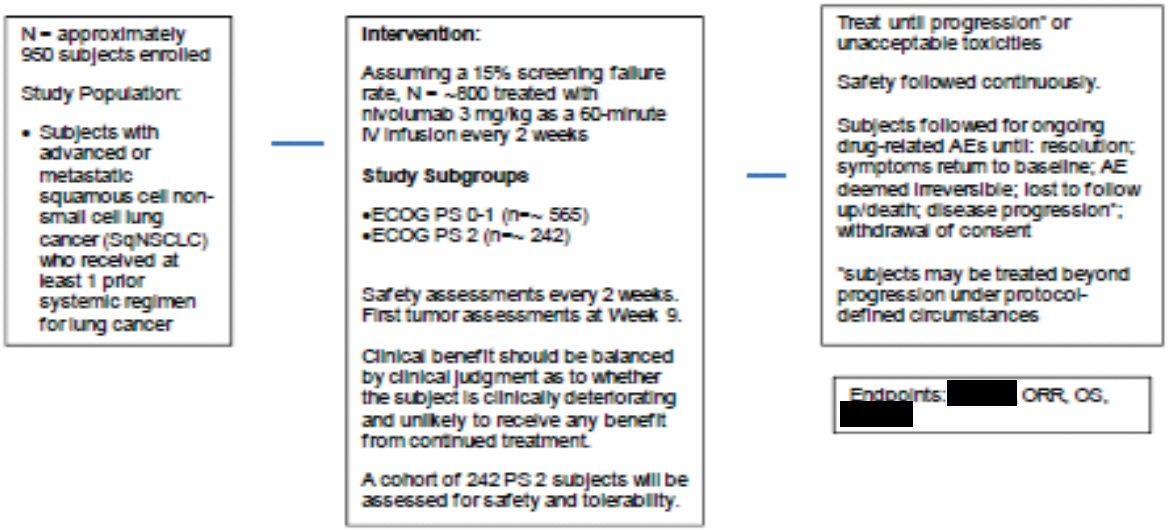
The Scientific Steering Committee (SSC) will provide guidance and scientific expertise on the clinical risk/benefit ratio closely following a defined Safety Management Plan.

Subjects will be evaluated in 2 separate subgroups: ECOG PS 0-1 subjects and PS 2 subjects. (Table 1.1)

Table 2.1-1: Subject Subgroup

(Subgroup Number)	Disease Criteria
Total study population n=950 Patients treated to be mentioned: 800	
Subgroup 1: ECOG PS 0-1 (N approximately 565)	• ECOG Performance Status 0 to 1 • Failed 1 or more prior systemic therapy • Balance enrolling second-line and third-line subjects
Subgroup 2: ECOG PS 2 (N approximately 242)	• ECOG Performance Status 2 • Failed 1 or more prior systemic therapy • Balance enrolling second-line and third-line subjects

Figure 2.1-1: Study Design



2.2 Treatment Assignment

After the subject's eligibility is established and informed consent has been obtained, the subject will be enrolled, and a number will be assigned through an interactive voice response system (IVRS). Specific instructions and procedures for using IVRS will be provided to the investigational site in a separate document/manual.

Subjects will be treated with 3 mg/kg of nivolumab as a 60-minute IV infusion (+/-5 min) on Day 1 +/- 2 of a treatment cycle every 2 weeks (14 days) until progression, unacceptable toxicity, or withdrawal of informed consent. No premedications are recommended for the initiation of dosing. Dosing calculations should be based on the body weight assessed at each visit. All doses should be rounded to the nearest milligram. The screening body weight may be used for dosing of Cycle 1. There will be no nivolumab dose escalations or reductions permitted. Subjects may be dosed no fewer than 12 days from the previous dose.

Subjects will be monitored continuously for AEs while on the study. Treatment modifications (eg, dose delay or discontinuation) will be based on specific laboratory and adverse event criteria.

2.3 Blinding and Unblinding

Not applicable. This is an open-label study.

2.4 Protocol Amendments

The protocol has 3 amendments issued. The table below summarizes the main purposes of these amendments. See amendments for further details.

Amendment #	Main purpose of the amendment
Amendment #1 21-Nov-2014	• The inclusion criteria have been expanded and the exclusion criteria have been minimized in order to expand the subject population. • The background section has also been updated to reflect the most recently available data. • The options for palliative local therapy have also been expanded to meet

	the needs of the current patient populations. • Randomization after 1 year to subjects who are still benefitting from treatment and achieved a partial or complete response to offer insight into the optimal treatment duration of nivolumab has been added. After 1 year of therapy, subjects will be randomized to continue nivolumab monotherapy (Cohort A) or discontinue therapy with the option of retreatment disease progression (Cohort B). • The requirement to have a separate assessment plan for the subjects in the Performance Status 2 (PS2) subgroup has been eliminated. • [redacted] • The Lung Cancer Symptom Survey has also been eliminated from the subject follow up and decreased while on treatment. • Initial tumor assessments have also been changed to occur at Week 8 instead of Week 6. • The statistical section has been reformatted. • The phrase "rate and frequency" has been changed to the term "incidence" throughout the protocol. • The term "Adverse Events of Special Interest" has been changed to "Select Adverse Events." • The Performance Status groups were renamed "Subgroup" (from "Cohort") to avoid confusion with the randomized cohorts.
Amendment #2 26-Feb-2015	• Study Director and Medical Monitor were changed • The use of a condom with spermicide was demoted from a highly effective to less effective method of contraception [redacted] • Pregnancy test had additional language added for clarification • Serum laboratory tests had additional footnote added for clarification
Amendment #3 18-Jun-2015	• Three key changes were made to this protocol: the sample size was reduced from 1800 to 950 (with 15% screening failure rate, 800 will be treated); second-line lung cancer patients will now be allowed to enroll in the study; and the randomization at one year into Cohort A and Cohort B has been removed.

The SAP is based on the revised protocol 03 incorporating amendment 3 dates 18Jun2015.

2.5 Data Monitoring Committee and Other External Committees

The SSC will closely review the safety data throughout the study to provide guidance and scientific expertise on the risk/benefit ratio in general and for the separate prospective subgroups following a predefined Safety Management Plan respecting the data for rate and frequency of Grade 3 and 4 select adverse events (estimated <25%) and QoL (patient-reported outcomes).

3 OBJECTIVES

3.1 Primary Objective

To determine the incidence of high-grade (CTCAE v4.0 Grades 3-4), treatment-related, select adverse events in subjects with advanced or metastatic SqNSCLC who progressed during or after at least 1 systemic therapy.

3.2 Secondary Objective

- To determine the incidence and to characterize the outcome of all high-grade (CTCAE v4.0 Grades 3-4), select adverse events in subjects with advanced or metastatic SqNSCLC who have progressed during or after at least 1 prior systemic therapy
- To estimate overall survival (OS) in all treated subjects
- To estimate investigator-assessed objective response rate (ORR)

[redacted]

4 ENDPOINTS

4.1 Primary Endpoints

The primary endpoint is the incidence of high-grade (CTCAE v4.0 Grades 3-4 or higher), treatment-related, select adverse events.

4.2 Secondary Endpoints

The secondary endpoints include:

- Incidence of high grade (Grade 3-4) select adverse events
- Median time to onset and median time to resolution (Grades 3-4) of select adverse events
- OS is defined as the time from first dosing date to the date of death. A subject who has not died will be censored at last known date alive. OS will be followed continuously while subjects are on treatment and every 3 months via in-person or phone contact after subjects discontinue the study drug.
- ORR is defined as the number and percentage of subjects with a best overall response (BOR) of confirmed CR or PR with respect to all treated subjects. ORR as assessed by the investigator will be reported.

[redacted]

[redacted]

5 SAMPLE SIZE AND POWER

The total sample size for this study is based on logistical considerations. Nevertheless, certain statistical properties of the projected sample size are indicated below.

A total of 950 subjects who are evaluated based on the ECOG PS will be enrolled, and a minimum of 30% (285 subjects) should present with PS2. In addition, a minimum of 40% of patients should be enrolled as second-line, and a minimum of 40% of patients should be enrolled as third-line. With a 15% screen failure rate, a total of approximately 800 subjects will be treated. If the true cumulative incidence rate is 0.5 then with n = 800 subjects, about 3 subjects will experience a rare adverse event (with a 95% confidence interval (CI) of 0.1%-1.3%) for the cumulative incidence rate. If the assumed true event rate is 0.3% then approximately 3 subjects will experience events with a 95% CI of 0.1%-0.8% for the assumed true event rate. In addition, with 800 subjects, the probability of observing at least one rare event (with 0.3% true rate) is 91.0%.

The 95% CI is calculated using the Clopper-Pearson method.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

See Core Safety SAP.

6.2 Treatment Regimens

Subjects will be treated with 3 mg/kg of nivolumab as a 60-minute IV infusion (+/-5 min) on Day 1 +/- 2 of a treatment cycle every 2 weeks (14 days) until progression, unacceptable toxicity, or withdrawal of informed consent. No premedications are recommended for the initiation of dosing. Dosing calculations should be based on the body weight assessed at each visit. All doses should be rounded to the nearest milligram. The screening body weight may be used for dosing of Cycle 1. There will be no nivolumab dose escalations or reductions permitted. Subjects may be dosed no fewer than 12 days from the previous dose.

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 any nivolumab. This is the primary population for safety and efficacy analyses.
- All response evaluable subjects: all treated subjects who have baseline and at least one on-study tumor measurement.

See section 7.1 for the subpopulation details.

7 STATISTICAL ANALYSES

7.1 General Methods

In the analysis described below (except where noted), counts and percentages will be reported for discrete variables with inclusion of unknown or missing values as a separate category. The mean, standard

deviation, median, range (minimum and maximum), and number of non-missing values will be reported for each continuous measure.

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

The time to event distribution (i.e overall survival and duration of response) will be estimated using Kaplan Meier techniques. Median for time to event endpoints along with 95% confidence interval (CI) will be constructed based on 95% CI using the Brookmeyer and Crowley method. OS rates at selected time points, including survival rates at Years 1 and 2, together with their 95% CIs will also be estimated using KM estimates on the OS curves. Associated 2-sided 95% CIs will be calculated using the Greenwood formula.

The analysis of primary, secondary (excluding objective response rate), and exploratory endpoints will be reported for the treated population and subgroups based on ECOG PS (PS 0-1 and PS 2). ORR will be reported for the response evaluable analysis set and by ECOG PS subgroups.

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

7.2 Study Conduct

7.2.1 Accrual

The accrual pattern will be summarized per country, investigational site and per month for all enrolled subjects. Informed consent date, first dosing date, country, and investigational site will be presented in a by subject listing of accrual.

7.2.2 Relevant Protocol Deviations

The relevant Protocol Deviations will be summarized for all enrolled subjects. The following programmable deviations from inclusion and exclusion criteria will be considered as relevant protocol deviations. Non-programmable relevant eligibility and on-treatment protocol deviations, as well as significant (both programmable and non-programmable) eligibility and on-treatment protocol deviations will be reported through data management listings.

<u>At entrance:</u>

- Subjects with any NSCLC histology other than squamous cell.

- Subjects without measurable disease at baseline.

- Subjects who did not meet prior therapy restrictions.

<u>On-study:</u>

- Subjects receiving concurrent anti-cancer therapy (defined as chemotherapy hormonal immunotherapy, radiation therapy, standard or investigational agents for treatment of NSCLC).

- Subjects treated differently from enrolled (subjects who received the wrong treatment, excluding the never treated).

A subject listing will also be produced.

7.3 Study Population

7.3.1 Subject Disposition

The total number of subjects enrolled in the study will be presented.

Number of subjects enrolled but not treated along with the reason will be tabulated. This analysis will be performed on the enrolled population only.

Number of subjects who discontinued study treatment along with corresponding reason will be tabulated using the enrolled population.

A subject listing for all enrolled subjects will be provided showing the subject's off study date and reason for going off-study. A subject listing for subjects not treated will also be provided, showing the subject's race, sex, age, consent date and reason for not being treated.

7.3.2 Demographic Characteristics

Demographic characteristics such as gender, age, race and ethnicity will be listed for all treated subjects. Demographic characteristics will also be summarized for all treated subjects.

The following characteristics will be summarized and listed:

- Age in years
- Age category (< 65, >= 65 to 75, >=75 to < 85, >=85, >=75, >=65 years)
- Gender, Race/Ethnicity
- ECOG PS (0-1, 2)
- Country
- Baseline weight
- Baseline height
- Baseline BMI
- Smoking Status
- Baseline Tumor Assessment
- Lung Cancer Symptom Score
- Baseline HIV result
- Baseline mutation status (EGFR, ALK, ROS, MET, KRAS, BRAF)
- CNS metastasis (Yes, No)
- Current disease stage (IIIB, IV)
- Cardiac insufficiency category by NYHA
- Type of prior cancer regimen (adjuvant, neo-adjuvant, metastatic disease)
- Time from diagnosis to enrollment
- Baseline Vital Sign (Temperature, BP, HR, RR) and Oxygen Saturation. Age will be calculated as follows: Age = maximum integer ≤ ([Date of informed consent – Date of Birth +1] / 365.25).

7.3.3 Medical history – Concurrent diseases

General medical history will be listed by subject and pretreatment events will be tabulated for all treated subjects.

7.3.4 Baseline Examinations

Subjects with abnormal baseline physical examination will be tabulated and listed by examination criteria using the treated population.

7.3.5 Prior Therapy Agent

Prior therapy will be summarized for all treated subjects.

The following information will be presented:

- Prior therapy (yes or no).
- Setting of prior systemic therapy regimen received (adjuvant, metastatic disease, neo-adjuvant).
- Best response to most recent prior regimen (CR/PR vs SD vs PD).
- Time from completion of most recent regimen to treatment (<3, 3-6, >6 months).
- Time from completion of prior adjuvant/neo-adjuvant therapy to treatment (subjects who received prior adjuvant/neo-adjuvant), (<6 months and >=6 months).
- Prior surgery related to cancer (yes or no)
- Prior radiotherapy (yes or no)
- Prior systemic therapy classified by therapeutic class and generic name
- Prior/current non-study medication classified by anatomic and therapeutic classes.

Agents and medication will be reported using the generic name. A listing by subject will also be provided for prior systemic cancer therapy, prior radiotherapy, prior surgery related to cancer and non-study medication.

7.4 Extent of Exposure

Analyses in this section will be performed in all treated subjects.

7.4.1 Administration of study therapy

The analysis of study drug exposure will focus on the on-study period. The first dosing day corresponds to the day of first administration of nivolumab. Throughout this analysis plan, nivolumab dose level will refer to the actual dose received rather than the planned dose. The dose level will be in mg/kg.

Subjects will be treated with 3 mg/kg of nivolumab as a 60-minute IV infusion (+/- 5 min) on Day 1+/-2 of a treatment cycle every 2 weeks (14 days) until progression, unacceptable toxicity, or withdrawal of informed consent.

The following parameters will be summarized (descriptive statistics) for all treated subjects:

- Relative dose intensity (%) using the following categories: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ⩾ 110%.
- Number of doses received (summary statistics)

- Cumulative dose
- Duration of treatment: duration of treatment will be presented using a Kaplan-Meier curve whereby the last dose date will be the event date for subjects who discontinued study therapy. Subjects who are still on study therapy will be censored on their last dose date. Also, duration of therapy will be presented according to the following: >3 months, >6 months, >9 months, and >12 months.

A by-subject listing of extent of exposure: weight, number of doses, date of first and last dose, duration of treatment, dose delay, reason for delay and reason for discontinuation.

Table 2: Administration of study therapy: definition of parameters

	nivolumab
Dosing schedule per protocol	3 mg/kg every 2 weeks
Dose	Dose (mg/kg) is defined as Total Dose administered (mg)/Most recent weight (kg). Dose administered in mg at each dosing date and weight is collected on the CRF.
Cumulative Dose	Cumulative dose (mg/kg) is sum of the doses (mg/kg) administered to a subject during the treatment period.
Relative dose intensity (%)	[Cumulative dose (mg/kg) /((Last dose date – Start dose date + 14) x 3/14] x 100
Duration of treatment	Last dose date – Start dose date +1

7.4.2 Modifications of Study Therapy

A dose will be considered as actually delayed if the delay is exceeding 3 days. It is defined as duration of previous cycle in days -14. Dose delays will be divided into the following categories: on-time, 4-7 days, 8-14 days, 15-42 days, >42 days. Reason for dose delay will be retrieved from CRF dosing pages.

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

The following parameters will be summarized:

- Number of subjects with at least one dose delayed
- Number of dose delayed per subject, length of delay, and reason for dose delay.
- Number of subject with at least one dose infusion interrupted along with reason for the interruptions and number of infusions interrupted per subject.
- Number of subjects with at least one infusion with IV rate reduced along with the reason of the rate reduction and number of IV rate reduced per subject.

[redacted]

7.5 Efficacy

7.5.1 Secondary Analyses

7.5.1.1 Overall Survival and Objective Response Rate

Overall survival is defined as the time between the start of treatment and the date of death due to any cause. A subject who has not died will be censored at last known date alive. OS will be followed up while subjects are on the study drug and every 3 months via in-person or phone contact after subjects discontinue the study drug.

Overall survival will be summarized using Kaplan-Meier (KM) product limit method for all treated subjects by subgroups based on ECOG PS (PS 0-1 and PS 2). Median values of OS, if estimable, along with 2-sided 95% CI using the Brookmeyer and Crowley method will be calculated. If medians are not estimable, other percentiles (eg, 10^{th} and 25^{th}) may be reported. OS rates at selected time points, including survival rates at Years 1 and 2, together with their 95% CIs will also be estimated using KM estimates on the OS curves. Minimum follow-up must be longer than the timepoint of interest to generate the OS rate for that particular timepoint. For example, if the timepoint of interest is 9 months and the interval of enrollment date and last patient last visit is less than 9 months, then, the minimum follow-up is not reached and OS rate is not generated. Associated 2-sided 95% CIs will be calculated using the Greenwood formula.

Objective Response Rate is defined as the number and percentage of subjects with a best overall response (BOR) of confirmed CR or PR. ORR as assessed by the investigator will be reported. The ORR will be summarized by binomial response rates and their corresponding two-sided 95% exact CIs using the Clopper-Pearson method. This analysis will be performed for all response evaluable subjects and by subject ECOG PS subgroups. In addition, the BOR will also be summarized according to response category. A by subject listing will be provided.

7.5.1.2 Subject Follow-up for OS

The extent of follow-up defined as the time between enrollment 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 subjects treated.

7.5.2 Other Efficacy Analyses

7.5.2.1 Follow-up Therapy

Subsequent therapy will be summarized and listed using the treated population.

- Chemotherapy by drug name
- Immunotherapy by drug name (including anti-PD1 or anti-CTLA4 agents)
- Tyrosine kinase inhibitor by drug name
- Other investigational agent by drug name
- Surgery
- Radiotherapy
- Any combination of the above

In addition, a by subject listing will also be presented for tumor response and lesion evaluation using the treated population.

7.6 Safety

Safety data will be presented for all treated subjects by ECOG PS subgroups (PS 0-1 and PS2) and worst grade per NCI CTCAE (any grade, grade 3-4, and grade 5). Safety and tolerability will be measured by the incidence of all adverse events, serious adverse events, deaths, and laboratory abnormalities. Adverse event assessments and laboratory tests will be performed at baseline, and continuously throughout the study at the beginning of each subsequent cycle.

7.6.1 Primary Analyses

7.6.1.1 High Grade Treatment-Related Select Adverse Events

The number and percentage of subjects who report high-grade (CTCAE v4.0 Grade 3 or higher), treatment-related, select adverse events (pulmonary, gastrointestinal, will be summarized using the safety set by system organ class and Medical Dictionary for Regulatory (MedDRA) preferred term.

7.6.1.2 Select Adverse Events

Categories of "select AEs" have been created to group together the most common and impactful preferred terms (PTs) by organ category, providing a better estimate of the frequency of similar kinds of organ-related AEs instead of using PTs only. These select adverse events are further defined as follows:

- may differ from or be more severe than AEs caused by non-immunotherapies
- may require unique (non-standard) intervention such as immunosuppressants (or hormone replacement therapy)
- early recognition and management may mitigate severe toxicity

The preferred terms included in the 'select AEs' category are those that are expected to be most commonly used to describe pneumonitis, interstitial nephritis, diarrhea/colitis, hepatitis, rash, and endocrinopathies. Hypersensitivity/infusion reactions are also considered a select AE category to facilitate the pooling of the most relevant preferred terms for analyses of hypersensitivity/infusion reaction events and not because such events fit the criteria for select AEs.

Select AEs are based on the list provided by BMS every 6 months.

Unless otherwise specified, analysis will be performed by select AE category and ECOG PS group: Some analyses may also be repeated by subcategory of endocrine events.

- Overall summary of any select AEs overall and by worst CTC grade presented by Category or Subcategory/PT A presentation of by age category will also be provided. Overall summary of drug-related select AEs by worst CTC grade presented by Category or Subcategory / PT
- Overall summary of any serious select AEs by worst CTC grade presented by Category or Subcategory /PT
- Overall summary of drug-related serious select AEs by worst CTC grade presented by Category or Subcategory /PT. A presentation of by age category will also be provided.
- Overall summary of serious select Endocrine AEs by worst CTC grade presented by Category or Subcategory /PT
- Overall summary of drug-related serious select Endocrine AEs by worst CTC grade presented by Category or Subcategory /PT
- Overall summary of any select AEs leading to discontinuation overall and by worst CTC grade presented by Category or Subcategory /PT

- Overall summary of drug-related select AEs leading to discontinuation overall and by worst CTC grade presented by Category or Subcategory /PT

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

By-subject select AE listing will be provided.

7.6.2 Secondary Analyses

7.6.2.1 Time-to onset of select AE

Time-to onset of the following specific events will be graphically displayed for each category/subcategory of select AEs using the Kaplan-Meier technique:

- Time-to onset of any grade select AE by ECOG PS subgroup
- Time-to onset of grade 3 to 5 select AE by ECOG PS subgroup
- Time-to onset of any grade drug-related select AE by ECOG PS subgroup
- Time-to onset of grade 3 to 5 drug-related select AE by ECOG PS subgroup

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

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

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

Time-to onset of the following specific events will be presented in a table for each category/subcategory of select AEs by ECOG PS subgroup:

- Summary of time to onset of select adverse events overall and by worst CTC grade presented by Category or Subcategory / PT
- Summary of time to onset of drug-related select adverse events overall and by worst CTC grade presented by Category or Subcategory / PT

7.6.2.2 Time-to resolution of select AE

Time to resolution of the following specific events will be summarized separately for each category/subcategory.

- Time-to resolution of select AE by ECOG PS subgroup
- Time-to resolution of drug-related select AE by ECOG PS subgroup

Time-to resolution analyses are restricted to treated subjects who experienced the specific events.

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

See time-to resolution definition subsection of APPENDIX 1 of the Core SAP for additional details.

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

[redacted]

[redacted]

7.6.4 Decimal Places

Decimal places should follow GBS General Requirements Statistical Outputs.

7.7 Interim Analyses

Not applicable.

7.8 Other Analyses

Other analyses include the percentage of subjects who received immune-modulating medication or hormone replacement therapy.

Additional exploratory analyses will be performed ad hoc and as necessary to address queries from the regulatory authorities.

8 CONVENTIONS

Unless otherwise noted, the following conventions should be understood to apply. Further conventions may be detailed in the Data Presentation Plan.

The duration between two dates will be calculated as [later date] – [earlier date] + 1 day. Study Day 1 or first dose date is the date of first study medication. Study day associated with an assessment will be calculated as [assessment date] – [first dose date (or randomization date for non-treated subjects)]. If the assessment is on or after first dose/randomization then 1 is added to the calculation.

The following factors will convert days to months or years: 1 month = 30.4375 days, 1 year = 365.25 days.

Conventions for Partial/Missing Dates

Unless specified otherwise the following conventions will be used for imputing partial dates:

- If only the day of the month is missing, the 15th of the month will be used to replace the missing day.
- If both the day and the month are missing, “July 1” will be used to replace the missing information.
- If a date is completely missing, it will be considered as missing.

For date of death:

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day*.
- If both the day and the month are missing, “Jan 1” will be used to replace the missing information*.

- If date is missing, death date will be imputed as the last known alive date.
  * The imputed death date will be compared with the last known alive date (date of censoring for survival). If the death date is not equal to the date of censoring for survival then the maximum of the (imputed death date, date of censoring for survival) will be considered as the date of death.

For date of progression:

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day*.
- If the day and month are missing or a date is completely missing, it will be considered as missing.
  * In case, the date of death is present (complete date), the imputed progression date will be compared with the date of death. The minimum of the (imputed progression date, date of death) will be considered as the date of progression.

For date of last tumor assessment:

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day*
- If the day and month are missing or a date is completely missing, it will be considered as missing.
  * In case, the date of death is present (complete date), the imputed date will be compared with the date of death. The minimum of the (imputed date, date of death) will be considered as the date of last tumor assessment.

For adverse events of special interest onset date:

- If only the day of the month is missing, the first 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.

For adverse events of special interest resolution date:

- If only the day of the month is missing, the last 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.

Otherwise, missing values will not in general be imputed.

9 CONTENT OF REPORTS

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

[redacted]

DOCUMENT HISTORY

Version Number	Date	[redacted]	Description
0.1	4 Sept 2015		Initial version
0.2	15 Oct 2015		Revision per BMS comments
0.3	20 Dec 2015		Revisions per BMS comments
1.0	15 Feb 2015		Revisions per client comments (version changed for finalization.)
1.1	17June2016		Revisions per Core SAP/DPP requirement
2.0	18July2016		Revisions per BMS comments