Statistical Analysis Plan for

Official Title of Study

A DOSE FREQUENCY OPTIMIZATION, PHASE IIIB/IV TRIAL OF NIVOLUMAB 240 MG EVERY 2 WEEKS VS NIVOLUMAB 480 MG EVERY 4 WEEKS IN SUBJECTS WITH ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER WHO RECEIVED 4 MONTHS OF NIVOLUMAB AT 3 MG/KG OR 240 MG EVERY 2 WEEKS CHECKMATE 384: CHECKPOINT PATHWAY AND NIVOLUMAB CLINICAL TRIAL EVALUATION 384

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STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

A DOSE FREQUENCY OPTIMIZATION, PHASE IIIB/IV TRIAL OF NIVOLUMAB 240 MG EVERY 2 WEEKS VS NIVOLUMAB 480 MG EVERY 4 WEEKS IN SUBJECTS WITH ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER WHO RECEIVED 4 MONTHS OF NIVOLUMAB AT 3 MG/KG OR 240 MG EVERY 2 WEEKS

CHECKMATE 384: CHECKPOINT PATHWAY AND NIVOLUMAB CLINICAL TRIAL EVALUATION 384

PROTOCOL(S) CA209384

VERSION # 3.0

TABLE OF CONTENTS

STATISTICAL ANALYSIS PLAN FOR CLINICAL STUDY REPORT 1
TABLE OF CONTENTS 2
LIST OF TABLES 5
LIST OF FIGURES 6
1 [redacted] 7
2 [redacted] 8
2.1 Study Design 8
2.2 Treatment Assignment 9
2.3 Blinding and Unblinding 10
2.4 Protocol Amendments 10
2.5 Data Monitoring Committee 11
3 OBJECTIVES 11
3.1 Primary 11
3.2 Secondary 11
3.3 [redacted]
4 ENDPOINTS 12
4.1 Primary Endpoints 12
4.2 Secondary Endpoints 13
4.3 [redacted] 13
4.3.1 [redacted] *13*
4.3.2 [redacted] *14*
5 SAMPLE SIZE AND POWER 14
6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES 15
6.1 Study Periods 15
6.1.1 Baseline period *15*
6.1.2 Post baseline period *15*
6.2 Treatment Regimens 15
6.3 Populations for Analyses 16
7 STATISTICAL ANALYSES 16
7.1 General Methods 16
7.2 Study Conduct 17

7.2.1 Accrual *17*
7.2.2 Relevant Protocol Deviations *17*
7.3 Study Population 18
7.3.1 Subject Disposition *18*
7.3.2 Demographics and Other Baseline Characteristics *18*
7.3.3 Medical history - Concurrent diseases *19*
7.3.4 Prior Therapy Agents *19*
7.3.5 Baseline examinations *20*
7.3.6 Stratification Factors *20*
7.4 Extent of Exposure 20
7.4.1 Administration of Study Therapy *20*
7.4.2 Modifications of Study Therapy *22*
7.4.2.1 Dose delays *22*
7.4.2.2 Dose Reductions/Escalations *22*
7.4.3 [redacted] *23*
7.4.4 Subsequent Therapy *23*
7.5 Efficacy 23
7.5.1 Primary Efficacy Analysis *23*
7.5.2 Secondary Efficacy Analyses *25*
7.5.3 Sensitivity Analysis *26*
7.5.4 Multiplicity Adjustment *27*
7.5.5 Efficacy Analyses By Subgroup *27*
7.6 Safety 27
7.6.1 Deaths *28*
7.6.2 Serious Adverse Events *28*
7.6.3 Adverse Events Leading to Discontinuation of Study Therapy *28*
7.6.4 Adverse Events Leading to Dose Delay *28*
7.6.5 Adverse Events *28*
7.6.6 Immune Mediated Adverse Events (IMAEs) *28*
7.6.6.1 Incidence of IMAE *30*
7.6.6.2 Time-to onset of IMAE *31*
7.6.6.3 Time-to resolution of IMAE *31*

7.6.7 Select Adverse Events 31
7.6.7.1 Incidence of select AE 32
7.6.7.2 Time-to onset of select AE 32
7.6.7.3 Time-to resolution of select AE 33
7.6.8 Other Events of Special Interest 34
7.6.8.1 Incidence of other events of special interest 35
7.6.8.2 Time-to onset of other events of special interest 36
7.6.8.3 Time-to resolution of other events of special interest 36
7.6.9 Immune modulating medication 37
7.6.10 Multiple Events 38
7.6.11 Clinical laboratory evaluations 38
7.6.11.1 Hematology 38
7.6.11.2 Serum Chemistry 38
7.6.11.3 Electrolytes 39
7.6.11.4 Additional Analyses 39
7.6.12 Vital Signs and Pulse Oximetry 39
7.6.13 Immunogenicity Analysis 39
7.6.14 Pregnancy 39
7.6.15 Clinical Safety Program (CSP) 39
7.6.16 Adverse Events By Subgroup 39
7.7 [redacted] 39
7.8 [redacted] 40
7.9 [redacted] .40
7.9.1 [redacted] 40
7.9.2 Calculation of Total Scores for Scales/Items 40
7.10 Interim Analyses 41
8 CONVENTIONS 41
9 CONTENT OF REPORTS 42
10 DOCUMENT HISTORY 43
11 [redacted] .45
APPENDIX 1 SELECT ADVERSE EVENTS DEFINITION AND CONVENTIONS 46

LIST OF TABLES

Table 2.4-1: Protocol Amendments 10
Table 4.1-1: Censoring Scheme for Primary Definition of PFS 12
Table 7.4.1-1: Administration of Prior Nivolumab Therapy Before Randomization: Definition of Parameters 21
Table 7.4.1-2: Administration of Study Therapy: Definition of Parameters 21
Table 7.6.8-1: Preferred Terms Included in Analysis of Other Events of Special Interest 34
Table 10-1: Document History 43
Table 11-1: Derivation of clustered select AE 47
Table 11-2: Select Adverse Events 49
Table 11-3: Revised IMAE Preferred Terms 53

LIST OF FIGURES

Figure 2.1-1: Study Schema 9
Figure 7.6.6-1: IMAE Classification Flowchart 29

[redacted]

2 STUDY DESCRIPTION

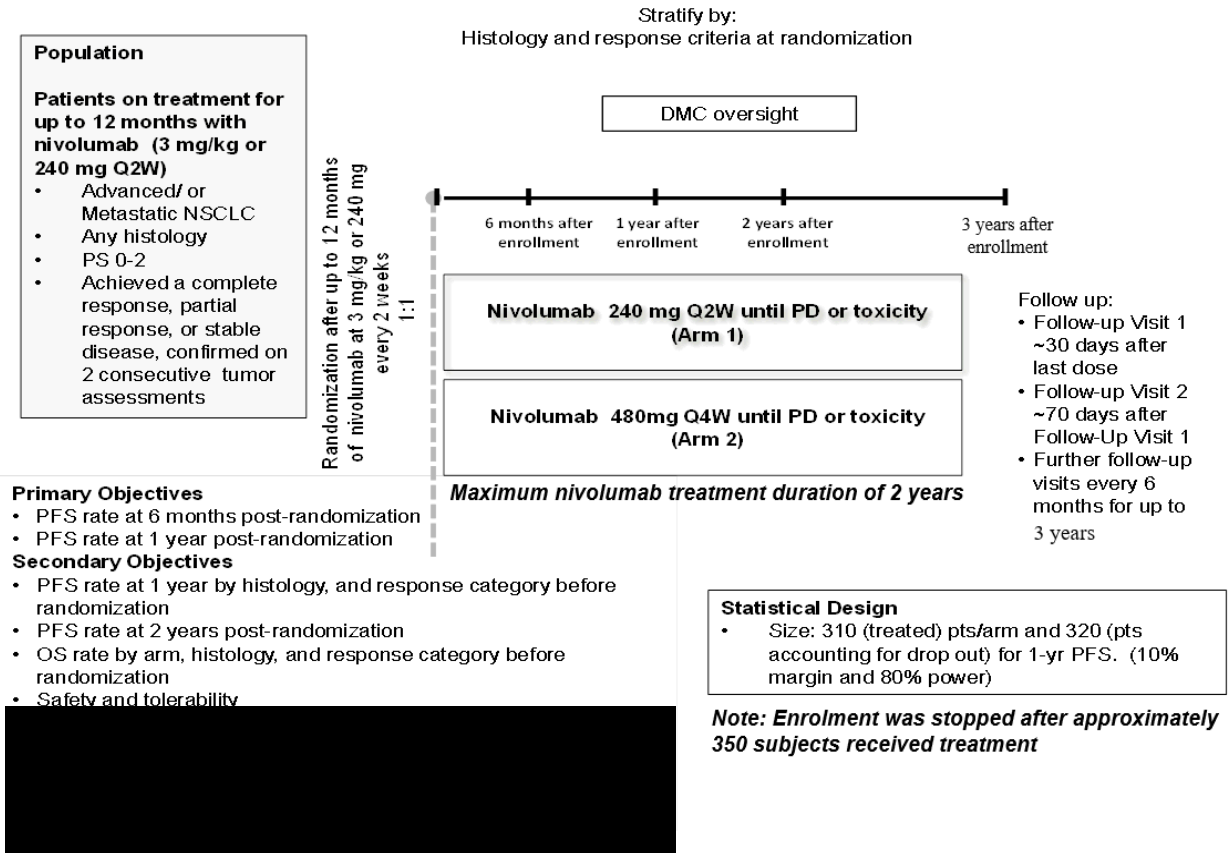
2.1 Study Design

This is an open-label, randomized phase IIIb/IV dose frequency optimization trial in adult patients with advanced/metastatic (Stage IIIb/IV) NSCLC (non-Sq and Sq). Subjects will have received approximately up to 12 months (52 weeks) of nivolumab therapy at either 3 mg/kg or 240 mg every 2 weeks and achieved a complete response (CR), partial response (PR), or stable disease (SD) as evidenced by 2 consecutive tumor assessments prior to enrollment. At enrollment, subjects will be randomized 1:1 to receive either 240 mg every 2 weeks (Arm 1) or 480 mg every 4 weeks (Arm 2). Randomization will be stratified by histology (Sq vs. Non-Sq) and response criteria to pre-study nivolumab at randomization (CR or PR vs. SD). For subjects receiving nivolumab 240 mg every 2 weeks, each 14-day dosing period will constitute a cycle. For subjects receiving nivolumab 480 mg every 4 weeks, each 28-day dosing period will constitute a cycle.

Subjects will continue treatment until disease progression or unacceptable toxicity for a maximum of 2 years from first randomized dose. The follow-up period begins when the decision to permanently discontinue a subject from study therapy is made (no further treatment or retreatment with nivolumab is anticipated). All subjects who discontinue study drug should comply with protocol specified follow-up procedures as outlined in Section 5 of the Clinical Protocol until death or the conclusion of the study. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely.

The study design schematic is presented in Figure 2.1-1.

Figure 2.1-1: Study Schema



Each patient's last study visit will be defined as the last on-treatment or follow-up visit that occurs prior to the date of 3 years after the initiation of randomized therapy. The study will be completed no later than 3 years after the last subject's first visit.

2.2 Treatment Assignment

CA209384 is a randomized study. 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 web-based response system (IWRS). Specific instructions for enrollment and randomization procedures using IWRS will be provided to the investigational site in a separate document/manual. Required information for registration includes but is not limited to the following:

- Response at randomization (CR or PR vs. SD)
- Tumour histology (Sq vs. Non-Sq)

Patients meeting all eligibility will be randomized to 1 of the 2 treatment arms. Randomization will be stratified by the following factors:

- Histology (Sq vs. Non-Sq)

- Response at randomization (CR or PR vs. SD)

2.3 Blinding and Unblinding

Not applicable. This is an open-label study.

2.4 Protocol Amendments

There are currently 4 approved amendments. Table 2.4-1shows the history of protocol amendment.

Table 2.4-1: Protocol Amendments

Document	Date	Summary of Changes
Amendment 1	11-Dec-2015	1. To allow the inclusion of subjects who are ineligible for or refuse chemotherapy in the first-line advanced non-small cell lung cancer setting and to use the flat dose instead of the weighted dose. 2. Human Immunodeficiency Virus testing at screening was also added for Germany sites only.
Revised Protocol 01	11-Dec-2015	Incorporates Amendment 01
Amendment 2	12-Feb-2016	Change the Human Immunodeficiency Virus criterion to reflect the language that is used across the nivolumab clinical development program and adjusted the frequency of magnetic resonance imaging scans in those with a history of brain metastasis to align with study assessments.
Revised Protocol 02	12-Feb-2016	Incorporates Amendment 02
Amendment 4	12-Aug-2016	1. Change the pre-study nivolumab requirement 2. Add a small increase to the sample size 3. Add immunogenicity as an endpoint 4. Make small changes to the laboratory and tumor assessments and duration of contraception use to align the protocol with updates to the nivolumab clinical development program.
Revised Protocol 03	12-Aug-2016	Incorporates Amendment 04
Revised Protocol 04	09-Feb-2018	1.Included additional language for nivolumab program level updates 2. Added information for interim analysis
Revised Protocol 05	26-Jun-2018	1. Reduced sample size and modified primary endpoint from non-inferiority to one-sided confidence interval around the differences of PFS rates. 2. Modified follow-up for overall survival for 3 years. 3. Added rationale for maximum treatment duration with nivolumab of 2 years.

2.5 Data Monitoring Committee

A Data Monitoring Committee (DMC) will be established to provide oversight of safety and efficacy (including assessment of 6 month PFS co-primary endpoint) considerations and to provide advice regarding actions the committee deems necessary for the continuing protection of enrolled patients and those yet to be recruited to the trial as well as for the continuing validity and scientific merit of the study results. The DMC is charged with assessing such actions in light of an acceptable benefit/risk profile for nivolumab.

One safety interim review will be conducted after 25 patients per treatment arm reach at least 3 months of treatment exposure after randomization. The DMC will review all available safety data and any available efficacy data that is provided. These efficacy data will be provided to allow evaluation of safety in the context of benefit. One formal interim review will be conducted at minimum of 6 months after the last patient's first visit. The DMC will review the analysis for 6-month PFS and OS as well as the safety data. In addition, it is anticipated that the DMC will meet at every 12 months or more frequently if deemed necessary for the duration of the trial to perform safety assessments.

3 OBJECTIVES

3.1 Primary

The coprimary objectives are to compare the PFS rate at 6 months after randomization and PFS rate at 1 year after randomization, as measured by investigator-assessed response using Response Evaluation Criteria in Solid Tumor (RECIST) 1.1 criteria, of nivolumab 240 mg every 2 weeks (Arm 1) and nivolumab 480 mg every 4 weeks (Arm 2) in subjects with advanced/metastatic (Stage IIIb/IV) NSCLC (non-Sq and Sq).

3.2 Secondary

The secondary objectives are:

- To compare PFS rate in Arms 1 and 2 at 1 year after randomization by tumor histology and by response criteria before randomization.
- To compare PFS rate at 2 years after randomization in Arms 1 and 2.
- To compare the OS rate at 1 year after randomization and up to 3 years after randomization in Arms 1 and 2, in all treated subjects, by tumor histology, and by response criteria before randomization.
- To assess safety and tolerability of nivolumab, as measured by the incidence and severity of AEs and specific laboratory abnormalities, in all treated subjects, in Arms 1 and 2, by tumor histology, and response criteria before randomization.

[redacted]

[redacted]

4 ENDPOINTS

4.1 Primary Endpoints

The coprimary endpoints of this trial will be assessed by PFS rate at 6 months after randomization and PFS rate at 1 year after randomization. PFS is defined as the time from the date of randomization to the date of first documented tumor progression determined by the investigator using RECIST 1.1 criteria or death due to any cause, whichever is earlier. Subjects who do not progress or die will be censored on the date of their last evaluable tumor assessment. Clinical deterioration in the absence of unequivocal evidence of progression (per RECIST 1.1) is not considered progression for purposes of determining PFS. Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who do not have any on-study tumor assessments and do not die will be censored on the date of randomization. Subjects who receive any subsequent anti-cancer therapy (including on-treatment palliative radio therapy [RT] of non-target bone lesions or central nervous system [CNS] lesions) without a prior reported progression will be censored at the last evaluable tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy.

Table 4.1-1: Censoring Scheme for Primary Definition of PFS

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments and no death	Randomization	Censored
No on study tumor assessments and no death	Randomization	Censored
New anticancer treatment started without a prior reported progression per RECIST 1.1 or death	Date of last evaluable tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy	Censored
Progression per RECIST 1.1 documented at scheduled or unscheduled visit and no new anticancer treatment started before	Date of the first documented tumor progression	Progressed
Subject progression free (per RECIST 1.1) and no new anticancer treatment started	Date of last tumor assessment	Censored
Death without prior progression per RECIST 1.1 and no new anticancer treatment started	Date of death	Progressed

RECIST: Response Evaluation Criteria in Solid Tumors

PFS rate at 6 months is the rate from Kaplan-Meier estimate 6 months after randomization; PFS rate at 1 year is the rate from Kaplan-Meier estimate at 1 year after randomization.

4.2 Secondary Endpoints

- PFS rate at 1 year after randomization by tumor histology (Sq vs. Non-Sq) and RECIST v1.1 response (CR or PR vs. SD) assessed before randomization
- PFS rate at 2 years after randomization
- OS rate at 1 year and OS rate up to 3 years after randomization by arm, tumor histology, and RECIST v1.1 response status at randomization (CR or PR vs. SD). OS is defined as time from the date of randomization to the date of death. Patients who did not die by the end of the study will be censored at the last known date alive. OS rate at 1 year is the rate from Kaplan-Meier estimated at one year after randomization.
- Safety and tolerability of nivolumab, as measured by incidence and severity of AEs and specific laboratory abnormalities.

Safety endpoints include adverse events (AEs) , serious adverse events (SAEs), AEs leading to discontinuation, AEs leading to dose delay, immune-mediated adverse events (IMAEs), select adverse events (select AEs), other events of special interest, and deaths. Adverse events will be coded and grouped into Preferred Terms (PT) by System Organ Class (SOC), using the most current version of Medical Dictionary for Regulatory Activities (MedDRA). The intensity of AEs will be graded 1 to 5 according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. The use of immune modulating concomitant medication will be also summarized. In addition specific clinical laboratory tests and vital signs will be analyzed.

[redacted]

5 SAMPLE SIZE AND POWER

The primary analyses evaluate the non-inferiority of post-randomization 6-month and 12-month milestone PFS rate of nivolumab 480 mg Q4W vs the PFS rate of nivolumab 240 mg Q2W in subjects with disease control (CR/PR/SD) after approximately up to 12 months (52 weeks) of nivolumab 3 mg/kg or 240 mg Q2W treatment. The non-inferiority margin of -10% was chosen for this study. Patients who received nivolumab for up to 12 months (52 weeks) and achieved CR, PR, or SD confirmed by 2 consecutive tumor assessments in the pre-study period will be randomized. Study CA209017 and CA209057 were used for estimating PFS rate at 6 months and 12 months. Patients who are either CR, PR or SD between months 3 and 12 were selected and their 6 month and 12 month PFS rate were estimated: the 12-month milestone PFS rate post-randomization is 0.48 with 240 mg Q2W and 6-month PFS rate post-randomization is 0.63.

The sample size was computed based on a cumulative hazard function which account for both progression and censoring distributions. Using cumulative hazard function and its relation with survival function, it is estimated that approximately 620 patients, 310 in each arm, will provide 80% power for the lower bound of a 95.2% one-sided confidence interval above -10% at the 12 month milestone and the lower bound of a 99.3% confidence interval above -10% at 6 months if PFS rates of the 2 arms are assumed to be equal. The experiment-wise error rate is maintained at one-sided 5% level.

To account for those who are randomized but do not receive treatment, 320 subjects per arm will be randomized. With a 15% screen failure rate, approximately 753 subjects will be screened to achieve approximately 640 randomized subjects.

Due to early stop of enrollment of the study, the sample size will be the number of subjects randomized after enrollment stops. Approximately 350 subjects are expected to be randomized and receive study treatment. With the significant reduction of sample size, there is insufficient power to demonstrate non-inferiority of the two treatment regimens. Hence, the adjustment of alpha between 6 months and 12 months PFS rates (as originally planned) will not be conducted. Instead, 95% one-sided confidence interval around the difference of PFS rates will be generated.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

6.1.1 Baseline period

Baseline evaluations or events will be defined as evaluations or events that occur before the date and time of the first dose of study treatment (or randomization date).

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

- Pre-treatment AEs will be defined as AEs with an onset date prior to but not including the day of the first dose of study treatment
- Baseline evaluations (physical examination, Eastern Cooperative Oncology Group (ECOG) Performance Status, laboratory tests and vital signs) will be defined as evaluations with a date (and time if collected) on or prior to the day (and the time if collected) of first dose of study treatment

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

6.1.2 Post baseline period

On-treatment AEs will be defined as AEs with an onset date-time on or after the date-time of the first dose of study treatment (or with an onset date on or after the day of first dose of study treatment if time is not collected or is missing). For subjects who are off study treatment, AEs will be counted as on-treatment if the events occurred within 100 days of the last dose of study treatment, unless otherwise specified.

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

Post-treatment AEs will be defined as AEs with an onset date-time 100 days after last dose of study treatment.

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

Post-treatment evaluations, if necessary, will be defined as evaluations taken 100 days after last dose of study treatment.

6.2 Treatment Regimens

The treatment group "**as randomized"** will be retrieved from the IWRS system

- Arm 1: nivolumab administered intravenously as a 30-minute (± 5 minutes) IV infusion on Day 1 of each treatment cycle at 240 mg every 2 weeks, until progression, unacceptable toxicity, withdrawal of consent, or the patient reaches a maximum of 5 years of treatment from the first on-study dose, or the study ends, whichever occurs first.
- Arm 2: nivolumab administered intravenously as a 30-minute (± 5 minutes) IV infusion on Day 1 of each treatment cycle at 480 mg every 4 weeks, until progression, unacceptable toxicity, withdrawal of consent, or the patients reaches a maximum of 5 years of treatment from the first on-study dose, or the study ends, whichever occurs first.

The treatment group "**as treated**" will be the same as the arm randomized by IWRS. However, if a subject receives the incorrect drug for **the entire period** of treatment, the subject's treatment group will be defined as the incorrect drug the subject actually received.

6.3 Populations for Analyses

- All enrolled subjects: All subjects who sign an informed consent form and are registered into the IWRS.
- All randomized subjects: All enrolled subjects who are randomized to 240 mg every 2 weeks or 480 mg every 4 weeks. This is the primary population for efficacy analyses. Analyses of demography and baseline characteristics, as well as outcome research, will be performed on this population, grouped as randomized.
- Per-protocol subjects: All randomized subjects who have no major protocol deviations. The relevant protocol deviations include the programmable deviations from inclusion and exclusion criteria at study entrance and administration of prohibited medications during the study. Non-programmable relevant eligibility and on-treatment protocol deviations, as well as significant (both programmable and non-programmable) eligibility including those subjects with untreated, symptomatic CNS metastases who should be excluded and on-treatment protocol deviations will be reported through a PPD tracking system - Clinical Trial Management System (CTMS). The details of relevant protocol deviations are described in Section 7.2.2. The primary efficacy endpoint will be analyzed for this population as a sensitivity analysis.
- All treated subjects: All randomized subjects who receive at least 1 dose of nivolumab. This is primary population for safety analyses.
- [redacted]

7 STATISTICAL ANALYSES

The following sections describe the statistical analyses in the study.

7.1 General Methods

Discrete variables will be summarized with the number and proportion of subjects falling into each category, grouped by treatment arm (with total). Percentages given in these tables will be rounded and therefore, may not always sum to 100%. Continuous variables will be summarized

using the mean, standard deviation (SD), median, minimum and maximum values (summary statistics) by treatment arm (with total). Corresponding by-subject listings will also be created for appropriate populations.

Time to event distribution (i.e. PFS and OS) will be estimated using Kaplan-Meier product-limit techniques. Median survival time along with two-sided 95% confidence interval (CI) will be constructed using Brookmeyer and Crowley method for each treatment arm. Rates at fixed time points (i.e. PFS at 6 months) will be derived from the Kaplan-Meier estimate and corresponding two-sided 95% confidence intervals will be derived for each treatment arm along with one-sided 95% CI for the difference between treatment arms based on Greenwood formula.

The stratified hazard ratio between the 2 treatment arms along with CI will be obtained by fitting a stratified Cox proportional hazard model with the treatment arm variable and stratification factors (tumour histology [Sq. vs. Non-Sq.] and response status at randomization [CR or PR vs. SD]).

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

7.2 Study Conduct

7.2.1 Accrual

The following will be summarized for all enrolled subjects:

- Number of subjects accrued by country and investigational site
- Number of subjects accrued by month.

A by-subject listing of accrual will be produced.

7.2.2 Relevant Protocol Deviations

The relevant protocol deviations will be summarized for all randomized subjects, by treatment arm and total. 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 including those subjects with untreated, symptomatic CNS metastases who will be excluded and on-treatment protocol deviations will be reported.

Eligibility at entrance:

- Subjects without histologically or cytological documented Sq.- or non-SqNSCLC who present with Stage IIIB/IV disease
- Subjects had received and tolerated nivolumab 3 mg/kg or 240 mg every 2 weeks for more than 12 months
- Subjects without at least 2 consecutive tumor assessments confirming CR, PR, or SD to the pre-study nivolumab treatment (latest scan must be performed within 28 days prior to randomization)

- Subjects without measurable disease by computed tomography (CT) or magnetic resonance imaging (MRI) per RECIST 1.1 criteria at the time of starting the first dose of pre-study nivolumab treatment
- Subject with baseline ECOG performance status > 2

On-Study:

- Subjects receiving concurrent antineoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of NSCLC)
- Subjects receiving immunosuppressive agents.
- Subjects receiving immunosuppressive doses of systemic corticosteroids (except as stated in the Clinical Protocol Section 3.4.3).
- Subjects receiving treatment other than the randomized treatment

A by-subject listing of relevant protocol deviations will also be produced.

7.3 Study Population

7.3.1 Subject Disposition

The total number of subjects enrolled (randomized or not randomized) will be presented along with the reason for not being randomized.

The number of subjects randomized but not treated along with the reason for not being treated will be tabulated by treatment arm as randomized. This analysis will be performed on the all randomized subjects only.

The number of subjects who discontinue treatment along with corresponding reason will be tabulated by treatment arm as treated.

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

7.3.2 Demographics and Other Baseline Characteristics

Descriptive statistics will be used to summarize the following demographics and baseline characteristics for all randomized subjects, as well as for per-protocol subjects, by treatment arm and total.

- Age (years)
- Age group (< 65, ≥ 65 - < 75, ≥ 75, ≥ 65)
- Gender, Race/Ethnicity, Region/ Country
- ECOG PS (0, 1, 2)
- Baseline weight (kg), height (cm)

- Baseline body mass index (BMI) (kg/m^2), which is calculated as (body weight in kilograms) / (height in meters)^2
- Tumor histology (Sq/Non-Sq)
- Disease stage at initial diagnosis (Stage 0/IA/IB/IIA/IIB/IIIA/IIIB/IV)
- Time from initial disease diagnosis to randomization (< 1 year, 1-< 2 year, 2 - < 3 year, 3 -< 4 year, 4 - < 5 year, ≥ 5 year)
- Cell type (Adenocarcinoma, Squamous Cell Carcinoma, Large Cell Carcinoma, Broncho-alveolar Carcinoma, Other)
- EGFR mutation status, ALK translocation status
- Tobacco use (current, former, never, unknown)
- All lesions (investigator tumor assessments at baseline): sites of disease, number of disease sites per subject
- Target lesions (investigator tumor assessments at baseline): presence of target lesions, site of target lesion, sum of diameters of target lesions.

7.3.3 Medical history - Concurrent diseases

General medical history will be reported as counts and percentages for all randomized subjects by treatment arm and total, and listed by subject.

7.3.4 Prior Therapy Agents

Prior therapy that was received prior to the nivolumab treatment before randomization will be summarized for all randomized subjects by treatment arm and total:

- Type of prior systemic therapy received
- Line of prior systemic therapies received (0, 1, 2, >=3)
- Setting of prior systemic therapy regimen received (adjuvant, metastatic disease, neo-adjuvant, locally advanced)
- Best response to prior systemic cancer therapy including adjuvant therapy or neo-adjuvant therapy (CR/PR vs. SD vs. PD)
- Best response to prior systemic cancer therapy in metastatic disease setting (CR/PR vs. SD vs. PD)
- Time from completion of most recent prior systemic cancer therapy to first dose of nivolumab treatment before randomization (< 3, 3 - < 6, ≥ 6 months)
- Time from completion of prior adjuvant/neo-adjuvant therapy to first dose of nivolumab treatment before randomization (subjects who received prior adjuvant/neo-adjuvant therapy), (< 6 months and ≥ 6 months)
- Prior surgery related to cancer (yes or no)

- Prior radiotherapy (yes/no, stop date, location)
- Time from completion of most recent prior radiotherapy to first dose of nivolumab treatment before randomization (<1, 1 - < 2, ≥ 2 months)
- Prior/current non-study medication classified by anatomic and therapeutic classes
- Prior systemic cancer therapy by therapeutic drug class and generic name.

Agents and medication will be reported using the generic name. A listing of prior systemic cancer therapy, radiotherapy and surgery related to cancer by subject will also be provided for all randomized subjects.

7.3.5 Baseline examinations

Subjects with abnormal baseline physical examination will be tabulated by examination criteria for all randomized subjects by treatment arm as randomized. A by-subject listing will be provided.

7.3.6 Stratification Factors

Summary tables by treatment arm for stratification factors (Histology [Sq vs. Non-Sq]; response criteria to pre-study nivolumab at randomization (CR or PR vs. SD) will be provided.

Summary tables (cross-tabulations) by treatment arm for stratification factor will be provided to show any discrepancies between what was reported through IWRS vs. CRF data (baseline).

7.4 Extent of Exposure

Analyses in this section will be performed by treatment arms as treated and in all treated subjects unless otherwise specified.

7.4.1 Administration of Study Therapy

Prior Nivolumab Therapy before Randomization

Prior to enrollment, subjects will have received up to 12 months (52 weeks) of nivolumab 3 mg/kg or 240 mg every 2 weeks (Q2W). The following parameters will be summarized (descriptive statistics) for prior nivolumab exposure before randomization for all randomized subjects:

- Relative dose intensity (%) using the following categories: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%.
- Number of infusions received (summary statistics)
- Duration of prior nivolumab treatment before randomization

Table 7.4.1-1 summarizes the key parameters used to calculate dosing data.

Table 7.4.1-1: Administration of Prior Nivolumab Therapy Before Randomization: Definition of Parameters

	Nivolumab
Dosing schedule per protocol	3mg/kg every 2 weeks; 240 mg every 2 weeks
Number of infusions	Number of infusions captured in prior systemic therapy Case Report Form (CRF)
Relative dose intensity (%)	[Number of infusions / {(Last dose date - Start dose date + 14) / 14}] x 100
Duration of treatment	Last dose date - Start dose date +1

On Treatment Nivolumab Therapy

At enrollment, subjects will be randomized to receive either 240 mg every 2 weeks (Arm 1) or 480 mg every 4 weeks (Arm 2). 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 will be presented by treatment arm 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.

A by-subject listing of extent of exposure: weight, number of doses, date of first and last dose, cumulative dose, and relative dose intensity, duration of treatment, and reason for discontinuation will be provided.

Table 7.4.1-2 summarizes the key parameters used to calculate dosing data.

Table 7.4.1-2: Administration of Study Therapy: Definition of Parameters

	Nivolumab
Dosing schedule per protocol	240 mg every 2 weeks for Arm1, 480 mg every 4 weeks for Arm 2
Dose	Dose administered in mg at each dosing date collected on the CRF.
Cumulative Dose	Cumulative dose (mg) is sum of the doses (mg) administered to a subject during the treatment period.
Relative dose intensity (%)	Arm1: [Cumulative dose (mg) /((Last dose date - Start dose date + 14)×240/14)] x 100

Table 7.4.1-2: Administration of Study Therapy: Definition of Parameters

	Nivolumab
	Arm2: [Cumulative dose (mg) /((Last dose date – Start dose date + 28) × 480/28)] × 100
Duration of treatment	Last dose date - Start dose date +1

7.4.2 Modifications of Study Therapy

7.4.2.1 Dose delays

Treatment may be delayed for up to a maximum of 6 weeks from the previous dose. Dose interruption of nivolumab which results in treatment interruption of >6 weeks will require treatment discontinuation, with the following exceptions: dosing interruptions to allow for prolonged steroid tapers to manage drug-related adverse events; dosing interruptions for non-drug-related reasons if approved by the medical monitor. Prior to re-initiating treatment in a subject with a dosing interruption lasting >6 weeks, the Medical Monitor must be consulted. A dose will be considered as actually delayed if the delay exceeds 2 days (i.e., greater than or equal to 3 days from scheduled dosing date). The length of delay is defined as (duration of previous cycle in days – 14) for Arm 1 and (duration of previous cycle in days – 28) for Arm 2. Dose delays will be divided into following categories: 3 - <8 days, 8 - <15 days, 15 - <28, 28 - <42, >=42 days. Reason for dose delay will be retrieved from the case report form (CRF) dosing pages.

The following parameters will be summarized by treatment arm:

- Number of dose delayed per subject, length of delay and reason for dose delay
- Number of subjects with at least one dose delay along with reason for the dose delay.

7.4.2.2 Dose Reductions/Escalations

There will be no dose escalations or reductions of nivolumab allowed. Subjects in Arm 1 may be dosed no less than 12 days from the previous dose; subjects in Arm 2 may be dosed no less than 26 days from the previous dose.

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 will be summarized by treatment arm:

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

A by-subject listing of study drug administered will be provided. A batch listing number will be also provided.

[redacted]

7.4.4 Subsequent Therapy

Subsequent therapies will be summarized and listed by:

- Frequency of subsequent therapy by type
- By-subject listing of subsequent therapy including all disease-related surgeries and radiotherapies

7.5 Efficacy

7.5.1 Primary Efficacy Analysis

The coprimary objectives will be assessed by PFS rate at 6 months and PFS rate at 12 months. PFS will be summarized by Kaplan-Meier product-limit method for all randomized patients. Median values of PFS, along with two-sided 95% CI using Brookmeyer and Crowley method (a log-log transformed CI for the survivor function S (t) [2, 3], will be calculated for each treatment arm.

The hazard ratios between treatment arms along with the one-sided 95% CI will be produced from a stratified Cox proportional hazard model (by tumour histology [Sq vs. Non-Sq] and response category at randomization [CR or PR vs. SD]).

PFS rates at 6 months and 12 months will be calculated using KM estimates on the PFS curve for each randomized treatment arm. Minimum follow-up must be longer than the time point to generate the rate. The two-sided 95% CIs, adjusted for stratifying factors (by tumor histology (Sq vs. Non-Sq), response criteria (CR or PR vs. SD) using inverse variance weight, for PFS rates at 6 months and 12 months will be calculated for each treatment arm, along with one-sided 95% CI for the difference between the two treatment arms using the Greenwood formula[4] for variance derivation. Denote $\hat{S}_i(t)$ as an estimate of survival function from Kaplan-Meier estimate and

$\hat{Var}(S_i(t))$ as the variance of estimation for stratum i at time t, respectively, w_i as the weight for stratum i, defined as $\frac{1/\hat{Var}(\hat{S}_i(t))}{\sum_{i=1}^{k}[1/\hat{Var}(\hat{S}_i(t))]}$ where k is the number of strata (k = 4). Then the weighted survival estimate for PFS rate across all the strata at time t is $\sum_{i=1}^{k} w_i \hat{S}_i(t)$ and weighted variance of estimation is $\hat{\sigma}_w^2 = \frac{1}{\sum_{i=1}^{k} 1/\hat{Var}(\hat{S}_i(t))}$. The two-sided 95% CIs for the PFS rates for each treatment arm will be calculated as $\sum_{i=1}^{k} w_i \hat{S}_i(t) \pm z_{(1-\alpha/2)} \times \hat{\sigma}_w$, where α=0.05.

The estimated PFS rate difference at time t between two treatment arms is $\hat{S}_{E_i}(t) - \hat{S}_{C_i}(t)$, where $\hat{S}_{Ei}(t)$ is the estimated PFS rate for 480 mg every 4 weeks treatment arm (Arm2) for stratum i and $\hat{S}_{C_i}(t)$ is the estimated PFS rate for 240 mg every 2 weeks treatment arm (Arm 1) for stratum i. The variance for PFS rate difference between two treatment arms at time t for stratum i is $\hat{Var}(\hat{S}_{E_i}(t)) + \hat{Var}(\hat{S}_{C_i}(t))$. Denote W_i as the weight for stratum i, defined as $\frac{1/[\hat{Var}(\hat{S}_{Ei}(t)) + \hat{Var}(\hat{S}_{Ci}(t))]}{\sum_{i=1}^{k}\left\{1/[\hat{Var}(\hat{S}_{Ei}(t)) + \hat{Var}(\hat{S}_{Ci}(t))]\right\}}$ where k is the number of strata (k = 4). Then the weighted estimate for PFS rate difference between two treatment arms across all the strata at time t is $\sum_{i=1}^{k} W_i(\hat{S}_{Ei}(t) - \hat{S}_{Ci}(t))$ and weighted variance of estimation is $\hat{\sigma}_W^2 = \frac{1}{\sum_{i=1}^{k} 1/[\hat{Var}(\hat{S}_{E_i}(t)) + \hat{Var}(\hat{S}_{C_i}(t))]}$. The one-sided 95% CIs for the difference of PFS rates between two treatment arms will be calculated as $(\sum_{i=1}^{k} W_i(\hat{S}_{Ei}(t) - \hat{S}_{Ci}(t)) - z_\alpha \times \hat{\sigma}_W,\ 1)$, where α=0.05.

The source of progression (death vs. progression) will be summarized by treatment arm.

The status of subjects who are censored in the PFS Kaplan-Meier analysis will be tabulated for each treatment group using following categories:

- On-study (on treatment, in follow-up)
- Off-study: (lost to follow-up, withdrew consent, other).
- No baseline tumor assessment and no death
- No on-study tumor assessment and no death

For the 6-month analysis, the 99.3% one-sided adjusted CI around the difference in PFS rates between two treatment arms will be generated using the inverse variance weight method as above where α=0.007. If the lower bound of the CI is above -10%, non-inferiority will be claimed.

A 95.2% adjusted CI around the difference in PFS rates at 12 months will be generated using the same approach for 6-month analysis where α=0.048. If the lower limit of the CI is above -10%, it is considered that the Arm 2 (Q4W) is non-inferior to Arm 1 (Q2W).

Due to the early stop of enrolment of the study, approximately 350 subjects are expected to be randomized and receive study treatment. With the significant reduction of sample size, there is insufficient power to demonstrate non-inferiority of the two treatment regimens. Hence, the adjustment of alpha between 6 months and 12 months PFS rates will not be conducted. Instead, 95% one-sided confidence interval around the difference of PFS rates will be generated.

7.5.2 Secondary Efficacy Analyses

PFS rate at 2 years and the corresponding two-sided 95% CI for each treatment arm, along with the one-sided 95% CI for the difference of PFS rate at 2 years between the treatment arms will also be calculated using the same method for PFS rate at 6 months described in the primary efficacy analysis.

OS will be summarized by KM product-limit method for all randomized patients. Median values of OS, along with two-sided 95% CI will be calculated for each treatment arm using the same method as for PFS. The hazard ratios between treatment arms along with the 95% CI will also be produced from a stratified Cox proportional hazard model as for PFS. Survival rates at 6, 12, 18, 24, and 36 months will be estimated for each treatment arm. Minimum follow-up must be longer than time point to generate the rate. The two-sided 95% CIs for OS rates at each time point for each treatment arm, along with the one-sided 95% CI for the difference of OS rates at each time point between two treatment arms will be calculated using the same method for PFS rates. OS rates at each time point and corresponding two-sided 95% CI for each treatment arm, along with the one-sided 95% CI for the difference of OS rates at each time point between the treatment arms will also be calculated adjusting for stratifying factors - tumor histology and response criteria using the inverse variance weight as for PFS rates.

The status of subjects who are censored in the OS Kaplan-Meier analysis will be tabulated for each treatment arm using following categories:

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

7.5.3 Sensitivity Analysis

The following sensitivity analysis will be conducted:

- Same analyses for PFS described in Section 7.5.1 will be repeated for per-protocol subjects
- The PFS rate at 6 months and 12 months will be calculated using KM estimates on the PFS curve for each randomized treatment arm. The two-sided unadjusted 95% CI for PFS rates at 6 months and 12 months for each treatment arm and the one-sided unadjusted 95% CI for the difference of PFS rates between two treatment arms will be calculated.
- For the 6-month analysis, the 99.3% one-sided unadjusted CI around the difference in PFS rates between two treatment arms will be generated. A 95.2% one-sided unadjusted CI around the difference in PFS rates at 12 months will also be generated. With the significant reduction of sample size due to the early stop of enrolment of the study, the adjustment of alpha between 6 months and 12 months PFS rates will not be conducted. Instead, 95% one-sided unadjusted confidence interval around the difference of PFS rates will be generated.
- OS rates at 36 months for each treatment arm and the difference of OS rates at each time point between two treatment arms will be estimated using KM method. The two-sided 95% CI for OS rates at each time point for each treatment arm and the one-sided 95% CI for the difference of OS rates at each time point between two treatment arms will be calculated using bootstrapping estimation method. Compute the Kaplan-Meier estimator for the bootstrap sample, $\hat{S}^{*}_{X}(t)$. Take 10000 bootstrap samples, and compute the Kaplan-Meier estimators for each bootstrap sample at the time point t. To be specific, let $\hat{S}^{*1}_{X}$, $\hat{S}^{*2}_{X}$,…, $\hat{S}^{*10000}_{X}$ be the corresponding estimations at time point t of the bootstrap samples. For two-sided 95% CI of OS rates within each treatment arm, sort the estimates in ascending order and select the values that cut off the lower and upper 2.5 percentiles to give lower and upper limit of 95% CI.

  For the difference of OS rates at time t between two treatment arms, let $\hat{S}^{*1}_{E} - \hat{S}^{*1}_{C}$, $\hat{S}^{*10000}_{E} - \hat{S}^{*10000}_{C}$ be the difference of OS rates between Arm 2 and Arm 1 for bootstrap sample 1, sample 10000. For one-sided 95% CI for the difference of OS rates between two treatment arms, sort the estimates in ascending order and select the value that cut off the lower 5 percentiles to give lower limit of 95% CI.
- Extent of follow-up for OS will be summarized for each treatment arm. Extent of follow-up will be assessed by the duration between randomization date and death date or last known date alive for subjects who are still alive.

7.5.4 Multiplicity Adjustment

The overall confidence level for the study in demonstrating non-inferiority is 95%, which is equivalent to 5% of Type I error. Type I error of 0.7% will be allocated for the 6 month analysis which is equivalent to 99.3% confidence interval. The final alpha depends on the observation of data and it is expected that 0.048 will keep the overall alpha level at 5% based on data from study 017 and 057. Type of I error of 0.048 is equivalent to a 95.2% confidence interval.

With the significant reduction of sample size due to the early stop of enrolment of the study, there is insufficient power to demonstrate non-inferiority of the two treatment regimens. Hence, the adjustment of alpha between 6 months and 12 months PFS rates will not be conducted. Instead, 95% one-sided confidence interval around the difference of PFS rates will be generated.

7.5.5 Efficacy Analyses By Subgroup

PFS rates at 6, 12 and 24 months and corresponding two-sided 95% CI for each treatment arm, along with the one-sided 95% CI for the difference of PFS rates at 6, 12 and 24 months between the treatment arms will be calculated for the following subgroups using the same method as for PFS rate described in the primary efficacy analysis.

- Gender (male vs. female)
- Age categorization (< 65 vs. ≥ 65)
- Baseline ECOG PS (0,1, 2)
- EGFR mutation status (positive vs. not detected vs. not reported)
- Line of prior therapy (first line vs. ≥ second line)
- Duration of prior Nivolumab treatment (< 3 months, 3 - < 6 months vs. ≥ 6 months)
- Stratification factors (Histology [Sq vs. Non-Sq]; response criteria to pre-study nivolumab at randomization (CR or PR vs. SD)

OS rates at 6, 12, 18, 24, and 36 months will also be summarized by treatment arms using the same method as for PFS rate described in the primary efficacy analysis for the above subgroups.

7.6 Safety

The evaluation of safety is based on the incidence of deaths, adverse events (AEs), serious adverse events (SAEs), AEs leading to discontinuation, AEs leading to dose delay, immune mediated adverse events (IMAEs), select AEs, other events of special interest, vital signs, and specific laboratory abnormalities (worst grade) in each treatment arm. Safety results will be summarized in all treated subjects by treatment arms and overall population unless otherwise specified. All AEs, SAEs, drug-related AEs, and drug-related SAEs will be summarized using the worst grade per NCI CTCAE v4.0 by system organ class and preferred term. Laboratory abnormalities including hematology, chemistry, liver function, thyroid function, and renal function will be summarized using worst grade per NCI CTCAE v4.0 criteria.

7.6.1 Deaths

See Core Safety SAP.

7.6.2 Serious Adverse Events

See Core Safety SAP.

7.6.3 Adverse Events Leading to Discontinuation of Study Therapy

See Core Safety SAP.

7.6.4 Adverse Events Leading to Dose Delay

AEs leading to dose delay will be summarized for all treated subjects by treatment arm:

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

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

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

7.6.5 Adverse Events

See Core Safety SAP.

In addition, a shift table of worst on-treatment CTCAE grade compared with baseline CTCAE grade per subject will be presented by PT. The analyses will be conducted using the 30-day safety window and repeated using the 100-day safety window.

7.6.6 Immune Mediated Adverse Events (IMAEs)

IMAEs are specific events defined as:

- Events occurring within 100 days of the last dose;
- Regardless of causality;
- With no clear alternate etiology based on investigator assessment, with data collected on a new CRF page;
- Treated with immune-modulating medication. (Of note, adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis are considered IMAEs regardless of immune-modulating medication use, since endocrine events are often managed without immune-modulating medication).

The IMAE data collection process is presented in Figure 7.6.6-1 and Table 11.3 provides the list of preferred terms that will be subject to evaluation as IMAEs.

7.6.6.1 Incidence of IMAE

See Core Safety SAP.

IMAEs will be summarized by treatment arm:

- Overall summary of IMAEs by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by Category/PT
- Overall summary of IMAEs by worst CTC grade (grade 1, 2, 3, 4, 5, unknown), where immune modulating medication was initiated, presented by Category/PT
- Overall summary of IMAEs by worst CTC grade (any grade, grade 3-4, grade 5), where immune modulating medication was initiated, presented by Category/PT
- Overall summary of any Endocrine IMAEs by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by Category/PT
- Overall summary of any Endocrine IMAEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category/PT
- Overall summary of serious IMAEs by worst CTC grade (any grade, grade 3-4, grade 5), where immune modulating medication was initiated, presented by Category/PT
- Overall summary of Endocrine serious IMAEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category/PT
- Overall summary of IMAEs leading to discontinuation by worst CTC grade (grade 1, 2, 3, 4, 5, unknown), where immune modulating medication was initiated, presented by Category/PT
- Overall summary of IMAEs leading to discontinuation by worst CTC grade (any grade, grade 3-4, grade 5), where immune modulating medication was initiated, presented by Category/PT
- Overall summary of Endocrine IMAEs leading to discontinuation by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by Category/PT
- Overall summary of Endocrine IMAEs leading to discontinuation by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category/PT
- Overall summary of IMAEs leading to dose delay by worst CTC grade (grade 1, 2, 3, 4, 5, unknown), where immune modulating medication was initiated, presented by Category/PT
- Overall summary of IMAEs leading to dose delay by worst CTC grade (any grade, grade 3-4, grade 5), where immune modulating medication was initiated, presented by Category/PT
- Overall summary of Endocrine IMAEs leading to dose delay by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by Category/PT
- Overall summary of Endocrine IMAEs leading to dose delay by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category/PT

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

By-subject IMAE listing will be provided.

7.6.6.2 Time-to onset of IMAE

See Core Safety SAP.

Time-to onset of the following IMAE will be summarized for each category by treatment arm:

- Time-to onset of any grade IMAE where immune modulating medication was initiated
- Time-to onset of grade 3 to 5 IMAE where immune modulating medication was initiated
- Time-to onset of any grade Endocrine IMAE
- Time-to onset of grade 3 to 5 Endocrine IMAE

The median time-to onset and range summary statistics will be reported.

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

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

7.6.6.3 Time-to resolution of IMAE

See Core Safety SAP.

Time to resolution of the following IMAE will be summarized for each category by treatment arm:

- Time-to resolution of any grade IMAE where immune modulating medication was initiated
- Time-to resolution of grade 3 to 5 IMAE where immune modulating medication was initiated
- Time-to resolution of any grade Endocrine IMAE
- Time-to resolution of grade 3 to 5 Endocrine IMAE

Time-to resolution analyses are restricted to treated subjects who experienced at least one IMAE from the Category. Time-to resolution where immune modulating medication was initiated analyses are restricted to treated subjects who experienced the specific events where immune modulating medication was initiated from the Category.

The following summary statistics will be reported: percentage of subjects with resolution of the longest duration of IMAEs, median time-to resolution (derived from Kaplan-Meier estimation) and ranges.

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

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

7.6.7 Select Adverse Events

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

7.6.7.1 Incidence of select AE

See Core Safety SAP.

Select AEs will be summarized for all treated subjects by treatment arms for each category/subcategory:

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

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

By-subject select AE listing will be provided.

7.6.7.2 Time-to onset of select AE

See Core Safety SAP.

Time-to onset of the following specific events will be summarized for each category/subcategory of select AEs by treatment arm:

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

The median time-to onset and range summary statistics will be reported.

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

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

7.6.7.3 Time-to resolution of select AE

See Core Safety SAP.

Time to resolution of the following specific events will be summarized separately for each category/subcategory by treatment arm:

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

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

Time-to resolution analyses are restricted to treated subjects who experience the specific events. Time-to resolution where immune modulating medication is initiated analyses are restricted to treated subjects who experience the specific events and who receive immune modulating medication during the longest select AE.

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

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

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

7.6.8 Other Events of Special Interest

Unless otherwise specified, analyses will be performed by other events of special interest category. Other events of special interest include the following categories: Myasthenic Syndrome, Demyelination event, Guillain-Barre Syndrome, Pancreatitis event, Uveitis event, Encephalitis event.

Table 7.6.8-1below provides a summary of the other events of special interest category and their respective PTs.

Table 7.6.8-1: Preferred Terms Included in Analysis of Other Events of Special Interest

Other Events of Special Interest Category	Preferred Terms included under Other Events of Special Interest Category
Myasthenic Syndrome	Myasthenia Gravis, Myasthenia Gravis Crisis, Myasthenic Syndrome
Demyelination Event	Autoimmune demyelinating Disease, Demyelination
Guillain-Barre Syndrome	Guillain-Barre Syndrome, Miller Fisher Syndrome
Pancreatitis Event	Autoimmune pancreatitis, Haemorrhagic Necrotic Pancreatistis, Pancreatitis, Pancreatitis Acute, Pancreatitis Necrotising

Table 7.6.8-1: Preferred Terms Included in Analysis of Other Events of Special Interest

Other Events of Special Interest Category	Preferred Terms included under Other Events of Special Interest Category
Uveitis Entve	Autoimmune Uveitis, Chorioretinitis, Cyclitis, Iridocyclitis, Iritis, Uveitis
Encephalitis Event	Acute Encephalitis with refractory, Repetitive Partial Seizures, Bickerstaff's Encephalitis, Encephalitis, Encephalitis Allergic, Encephalitis Autoimmune, Encephalitis Brain Stem, Encephalitis Haemorrhagic, Encephalitis Lethargica, Encephalitis Toxic, Lupus Encephalitis, Noninfective Encephalitis, Panencephalitis, Rasmussen Encephalitis, Subacute Sclerosing Panencephalitis

7.6.8.1 Incidence of other events of special interest

See Core Safety SAP.

Other events of special interest will be summarized for all treated subjects by treatment arm:

- Overall summary of other events of special interest by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by Category/PT
- Overall summary of other events of special interest by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category/PT
- Overall summary of drug-related other events of special interest by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by Category/PT
- Overall summary of drug-related other events of special interest by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category/PT.
- Overall summary of serious other events of special interest by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by Category/PT
- Overall summary of other events of special interest leading to discontinuation by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by Category/PT
- Overall summary of other events of special interest that required immune modulating medication by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by Category/PT
- Overall summary of other events of special interest that required immune modulating medication by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category/PT
- Overall summary of drug-related other events of special interest that required immune modulating medication by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by Category/PT

- Overall summary of drug-related other events of special interest that required immune modulating medication by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category/PT

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

By-subject other events of special interest listing will be provided.

7.6.8.2 Time-to onset of other events of special interest

See Core Safety SAP.

Time-to onset of the following other events of special interest will be summarized for each category by treatment arm:

- Time-to onset of any grade other events of special interest
- Time-to onset of grade 3 to 5 other events of special interest
- Time-to onset of any grade drug-related other events of special interest
- Time-to onset of grade 3 to 5 drug-related other events of special interest
- Time-to onset of any grade other events of special interest where immune modulating medication was initiated
- Time-to onset of grade 3 to 5 other events of special interest where immune modulating medication was initiated

The median time-to onset and range summary statistics will be reported.

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

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

7.6.8.3 Time-to resolution of other events of special interest

See Core Safety SAP.

- Time-to resolution of any grade other events of special interest
- Time-to resolution of grade 3 to 5 other events of special interest
- Time-to resolution of any grade drug-related other events of special interest
- Time-to resolution of grade 3 to 5 drug-related other events of special interest
- Time-to resolution of any grade other events of special interest where immune modulating medication was initiated
- Time-to resolution of grade 3 to 5 other events of special interest where immune modulating medication was initiated

Time-to resolution analyses will be restricted to treated subjects who experience the other events of special interest. Time-to resolution where immune modulating medication is initiated analyses

will be restricted to treated subjects who experience the other events of special interest and who receive immune modulating medication during the longest other events of special interest.

The following summary statistics will be reported: percentage of subjects who experienced the other events of special interest, percentage of subjects with resolution of their other events of special interest of longest duration, median time-to resolution (derived from Kaplan-Meier estimation) and ranges.

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

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

7.6.9 Immune modulating medication

The percentage of subjects who receive immune modulating concomitant medication for

- management of adverse event
- other use

will be reported separately for each treatment arm (percentages of treated subjects by medication class and generic term).

Management of select AEs

For each category/subcategory of select AEs (see Table 11-2), the following will be reported for each treatment arm:

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

These analyses will be performed on any select AEs, drug-related select AEs, select endocrine AEs and drug-related select endocrine AEs.

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

Management of IMAEs

For each category of IMAEs, the following will be reported for each treatment arm:

- Percentage of subjects who receive immune modulating concomitant medication for management of IMAE in the category among subjects who experience at least one IMAE in the category.
- The total duration of immune modulating concomitant medication for IMAE management.

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

Management of other events of special interest

For each category of other events of special interest, the following will be reported for each treatment arm:

- Percentage of subjects who receive immune modulating concomitant medication for management of other events of special interest in the category among subjects who experience at least one other event of special interest in the category.
- The total duration of immune modulating concomitant medication for other events of special interest management.

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

7.6.10 Multiple Events

The following summary tables will be provided for all treated subjects by treatment arms:

- A table showing the total number and rate (exposure adjusted) of occurrences of all AEs.
- A table showing the total number and rate (exposure adjusted) of occurrences for all AEs with an incidence at least 5% in any treatment arm.

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

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

For select AEs:

- A table showing the number of subjects experiencing an AE once or multiple times in each treatment arm

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

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

7.6.11 Clinical laboratory evaluations

The analysis population for each laboratory test is restricted to treated subjects who undergo that laboratory test.

7.6.11.1 Hematology

See Core Safety SAP.

7.6.11.2 Serum Chemistry

See Core Safety SAP

7.6.11.3 Electrolytes

See Core Safety SAP.

7.6.11.4 Additional Analyses

See Core Safety SAP.

7.6.12 Vital Signs and Pulse Oximetry

See Core Safety SAP

7.6.13 Immunogenicity Analysis

Definitions and analyses of immunogenicity are described in the core/integrated SAP for immunogenicity data of nivolumab document.

7.6.14 Pregnancy

See Core Safety SAP.

7.6.15 Clinical Safety Program (CSP)

Not applicable.

7.6.16 Adverse Events By Subgroup

Overall summary of drug-related AEs, drug-related serious AEs, and drug-related AEs leading to discontinuation by worst CTC grade (any grade, grade 3-4, grade 5) will be presented by SOC/PT and for each treatment arm for the following subgroups using the 100-day safety window:

- Gender (male vs. female)
- Age categorization (< 65 vs. ≥ 65)
- Baseline ECOG PS (0, 1, 2)
- Line of prior therapy (first line vs. ≥ second line)

An overall summary of immune modulating AEs by worst CTC grade (grade 1, 2, 3, 4, 5) will be presented by immune mediated category/PT and for each treatment arm for the above subgroups using the 100-day safety window.

In addition to the above subgroup analyses, a summary of serious AEs by worst CTC grade (any grade, grade 3-4, grade 5) and a summary of immune modulating AEs by worst CTC grade (grade 1, 2, 3, 4, 5) will be presented for the subgroups defined by duration of prior Nivolumab treatment (< 3 months, 3 - < 6 months vs. ≥ 6 months).

[redacted]

[redacted]

[redacted]

7.10 Interim Analyses

The first safety interim analysis will be conducted after 25 subjects per treatment arm with at least 3 months of treatment exposure after randomization. It is anticipated that the DMC will meet at every 6 months to perform safety assessments.

In addition to the interim analyses specified above, additional interim analyses might be conducted, for example, to address regulatory questions or requests.

8 CONVENTIONS

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

- For missing and partial AE onset dates, imputation will be performed using the Adverse Event Domain Requirements Specification.
- For missing and partial AE resolution dates, imputation will be performed as follows:
  - 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 Section 4.3.3 of BMS Non-Study Medication Domain Requirements Specification.

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

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day. The imputed date will be compared to the last known date alive + 1 day and the maximum will be considered as the death date.
- If the month or the year is missing, the death date will be imputed as the last known date alive + 1 day.
- If the date is completely missing but the reason for death is present the death date will be imputed as the last known date alive + 1 day

For the date of progression, the following conventions will be used for imputing partial dates:

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day*.
- If the day and month are missing or a date is completely missing, it will be considered as missing.

* In the case of the date of death being present and complete, the imputed progression date will be compared to the date of death. The minimum of the imputed progression date and date of death will be considered as the date of progression.

For other partial/missing dates, the following conventions will be used:

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

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

Duration (e.g. time from first diagnosis of NSCLC to randomization, 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.

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

9 CONTENT OF REPORTS

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

10 DOCUMENT HISTORY

Table 10-1: Document History

Version Number	Author(s)	Description
1.0	[redacted]	Initial Approval June 20, 2016
2.0	[redacted]	Based on the protocol amendment 3, the following changes were made: 1. Change the pre-study nivolumab requirement 2. Add a small increase to the sample size 3. Add immunogenicity as an endpoint 4. For the first interim analysis, replace 100 patients per arm with 25 patients per arm and add safety DMC every 6 months. 5. IMAE definition was updated and updated IMAE preferred term list was updated. 6. PFS rates at 6, 12 and 24 months by duration of prior nivo treatment (<3 months, ≥3-<6 months and ≥6 months; as well as OS rates at 6, 12, 18, 24, 36, 48 and 60 months. 7. Analysis of PFS and OS rate adjusting for stratification factors with inverse variance weight 8. Bootstrap analysis for OS for years 3, 4, and 5 9. For the first interim analysis, replace 100 patients per arm with 25 patients per arm. Add safety DMC every 6 months. 10. By duration of pre-randomization nivolumab treatment (i.e. <3 months, ≥3-<6 months and ≥ 6 months) is added for IMAE and serious AE. 11. Added per protocol population with details.
	[redacted]	Based on the protocol amendment 4, section 7.10 interim analyses were updated.
3.0	[redacted]	Based on revised protocol 05, the following changes were made: 1. Reduced sample size and modified primary endpoint from non-inferiority to one-sided confidence interval around the differences of PFS rates. 2. For sensitivity analysis of PFS rates at 6-month and 12-month, alpha adjustment will not be conducted. Instead, 95% one-sided confidence interval around the difference of PFS rates will be done. 3. Modified follow-up for overall survival for 3 years. For secondary endpoint, OS rates were updated up to 3 years. 4. Added rationale for maximum treatment duration with nivolumab of 2 year.

Table 10-1: Document History

Version Number	Author(s)	Description
		5. Update the dose delay definition. As per protocol schedule, +/- 2 days are allowed visit window.

[redacted]

APPENDIX 1 SELECT ADVERSE EVENTS DEFINITION AND CONVENTIONS

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

For information, the select AEs defined at the time of finalization of the first version of the document are listed in Table 11-2 using MedDRA version 16. The updated list of select AEs will be used at the time of analysis and the final list used for the clinical study report will be included in an Appendix of the CSR.

Time-to onset definition

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

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

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

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

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

Time-to resolution definition

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

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

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

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

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

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

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

Table 11-1: Derivation of clustered select AE

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

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

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

1) Multiple adverse event records have the same onset date.

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