Official Title of Study:

AN OPEN-LABEL, SINGLE-ARM PHASE II SAFETY STUDY OF NIVOLUMAB IN PARTICIPANTS WITH ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER WHO HAVE PROGRESSED DURING OR AFTER RECEIVING AT LEAST ONE PRIOR SYSTEMIC REGIMEN

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STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

AN OPEN-LABEL, SINGLE-ARM PHASE II SAFETY STUDY OF NIVOLUMAB IN PARTICIPANTS WITH ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER WHO HAVE PROGRESSED DURING OR AFTER RECEIVING AT LEAST ONE PRIOR SYSTEMIC REGIMEN

PROTOCOL(S) CA209907

VERSION # 1.1

DATE: APRIL 8, 2019

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1 BACKGROUND AND RATIONALE

A less frequent administration of nivolumab has the potential for improved convenience for patients and reduce administrative burden. A flat dosing is expected to reduce prescription dosing errors, shorten pharmacy preparation time, and improve ease of administration. Extending the dosing interval to 4 weeks would provide increased flexibility between clinical visits, as compared to Q2W dosing schedule.

A dose of 480 mg Q4W was selected based on equivalence to the approved 3 mg/kg every 2 weeks at the median body weight of ~80 kg in nivolumab-treated participants. A PPK model predicted overall nivolumab average exposures across participants with a wide range of body weight from 480 mg Q4W to be similar to that from 3 mg/kg Q2W. Although the flat dose is expected to lead to higher exposure in lighter patients, relative to the exposure in heavier patients given the relationship between nivolumab PK and body weight, the predicted median and 95th percentile of exposures are maintained below those in 10 mg/kg every 2 weeks, which was established as a safe and well-tolerable dose across multiple tumor types. With a well-established understanding of NIVO clinical pharmacology, robust clinical data across multiple tumor types and well-characterized Exposure-Response relationships for efficacy and safety, the benefit-risk profile of Nivolumab 480 mg Q4W is predicted to be similar to 3 mg/kg Q2W across multiple tumor types. Therefore, a 480 mg Q4W is expected to be safe and tolerable and is included in NIVO clinical trials across multiple tumor types.

CA209907 is an open-label, single arm Phase 2 safety study of less frequent flat dose administration of nivolumab, 480 mg administered every 4 weeks, in participants with advanced or metastatic non-small cell lung cancer who have progressed during or after receiving at least 1 prior systemic regimen.

This document describes the statistical analyses that will be conducted for the clinical study report (CSR) of study CA209907. This document also refers to the Core Safety Statistical Analysis Plan[1] that contains program level safety analyses descriptions.

Research Hypothesis:

The safety profile of less frequent dosing regimen of 480 mg of nivolumab every 4 weeks is expected to be similar to that of 3 mg/kg of nivolumab every 2 weeks in participants with advanced or metastatic NSCLC. The analyses to summarize incidence of treatment-related select adverse events will be descriptive.

2 STUDY DESCRIPTION

2.1 Study Design

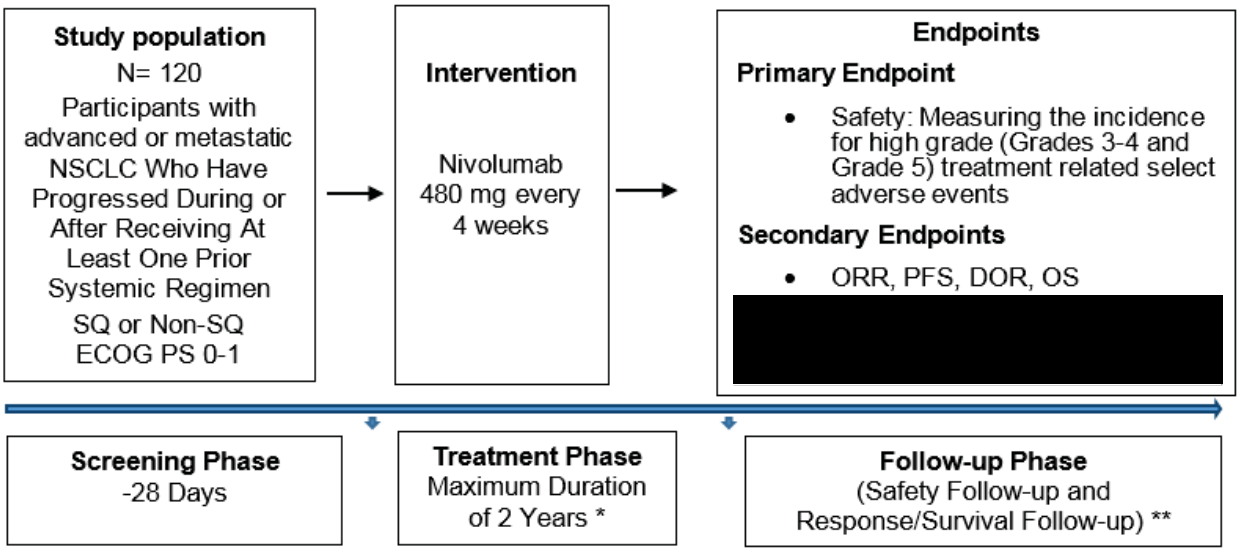
This is an open-label, single arm Phase 2 safety study of less frequent flat dose administration of nivolumab in participants ≥ 18 years old with advanced or metastatic non-small cell lung cancer who have progressed during or after receiving at least 1 prior systemic regimen. Nivolumab

480 mg will be administered every 4 weeks. Each 28-day dosing period will constitute a cycle. Participants will receive treatment with nivolumab every 4 weeks until progression, unacceptable toxicity, withdrawal of consent, death or a maximum of 2 years, whichever occurs first. Treatment beyond initial investigator-assessed RECIST 1.1-defined progression will be considered in participants experiencing investigator assessed clinical benefit and tolerating study therapy. The post-treatment follow-up begins when the decision to discontinue a participant from treatment is made. Participants who discontinue treatment for reasons other than disease progression will continue to have tumor assessments (if clinically feasible) according to the schedule.

The present study will treat approximately 120 participants. Participants will receive treatment 480 mg nivolumab every 4 weeks until progression, unacceptable toxicity, withdrawal of consent, death, or a maximum of 2 years, whichever occurs first.

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

Figure 2.1-1: Study Design Schema



* Nivolumab to be administered as a flat dose, 480 mg every 4 weeks, until progression, unacceptable toxicity, withdrawal of consent, or a maximum treatment duration of 2 years, whichever comes first.

** Participants discontinuing treatment earlier than 2 years will continue to be followed for survival follow up every **3 months** until death, lost to follow-up, or withdrawal of study consent or maximum duration of 2 years from start of study treatment whichever occurs first.

2.2 Treatment Assignment

Study will use Interactive Response Technology (IRT): All participants will be assigned using an Interactive Response Technology (IRT). Before the study is initiated, each user will receive log-in information and directions on how to access the IRT.

After the subject's initial eligibility is established and informed consent has been obtained, the subject must be enrolled into the study by using IRT to obtain the subject number. Every subject that signs the informed consent form must be assigned a subject number in IRT.

2.3 Blinding and Unblinding

Not applicable.

2.4 Protocol Amendments

This SAP incorporates the following amendments:

Table 2.4-1: Protocol Amendments

Amendment	Date of Issue	Summary of Major Changes
Revised Protocol 01 (Incorporate Administrative Letters 01 and 02)	10-Jan-2018	• Increased number of participants in study and sample size determination in statistical section [redacted] • Included additional language for nivolumab program level updates

2.5 Data Monitoring Committee

The Sponsor of this study will not utilize an independent data safety monitoring board (DSMB). BMS will assign a physician responsible for reviewing, on a systematic and continuous basis, the safety of participants in this study. This includes a review of serious and non-serious adverse events and all hematological and non-hematological events. In addition, BMS has a Medical Surveillance Team (MST), independent from the clinical medical monitor. The MST has the primary responsibility within Bristol-Myers Squibb for assessing emerging safety trends, identifying potential safety signals, notifying appropriate stakeholders of relevant findings, and implementing risk mitigation activities to ensure the safety of patients participating in BMS trials. The MST is also responsible for reviewing data from all sources including non-clinical studies and clinical trials, monitoring the progress of various nivolumab safety support activities, and recommending and implementing necessary changes to the safety plan and any other specific safety-related activities.

3 OBJECTIVES

3.1 Primary

- To characterize the safety of nivolumab 480 mg IV over 30 minutes every 4 weeks

3.2 Secondary

- To estimate the efficacy of nivolumab 480 mg IV over 30 minutes every 4 weeks

[redacted]

4 ENDPOINTS

4.1 Primary Endpoint

4.1.1 Safety

The primary endpoint of the study is the rate of participants who experience high-grade (worst CTC Grade 3, 4 or 5), drug-related, select Adverse Events (select AEs). The drug-related Grade 3 - 5 select AE rate is defined as number of participants who experienced at least 1 select AE of Grade 3 or higher, judged to be related to study drug by the investigator, and with onset on or after the first dose of study treatment and within 30 days (100 days for sensitivity analysis) of the last dose of study treatment, divided by number of treated participants. AE grade will be defined using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0 criteria.

The select AEs consist of a list of preferred terms grouped by specific category (eg, pulmonary events, gastrointestinal events, hepatic events, renal events, skin events, endocrine events categories) and by subcategory (eg, thyroid disorders, diabetes, pituitary, adrenal disorder 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. Drug-related AEs are those events with relationship to study drug "Related" as recorded on the CRF. If the relationship to study drug is missing, the AE will be considered as drug-related. This study will also evaluate the incidence of infusion reactions when nivolumab 480 mg is administered by IV infusion over 30 minutes.

Overall safety and tolerability will be measured by the incidence of adverse events (AEs), serious adverse events (SAEs), AEs leading to discontinuation, adverse events leading to dose delay, immune-mediated AEs (IMAEs), infusion reactions, other events of special interest, deaths, specific laboratory abnormalities (worst grade). See details in the Core Safety SAP.

4.2 Secondary Endpoints

4.2.1 Progression-Free Survival

Two definitions are used for analysis of Progression-Free Survival (PFS). The primary definition accounts for subsequent therapy by censoring at the last evaluable tumor assessment on or prior to the date of subsequent therapy. The secondary definition is irrespective of subsequent therapy and does not account for subsequent therapy.

Clinical deterioration in the absence of unequivocal evidence of progression (per RECIST v1.1 criteria) is not considered progression for purposes of determining PFS.

PFS rate at time *T* is defined as the probability that a subject has not progressed and is alive at time *T* following randomization. PFS rates at fixed time points (e.g. 6 months, depending on the minimum follow-up) are defined as the probability that a subject has not progressed and is alive at time *T* following randomization.

The first on-study tumor assessment is scheduled to be conducted at 12 weeks (± 1 week) following randomization. Subsequent tumor assessments are scheduled every 6 weeks (± 1 week) up to 13 months, then every 12 weeks until disease progression.

4.2.1.1 Primary Definition of Progression-Free Survival (Accounting for Subsequent Therapy)

The primary definition of PFS (PFS truncated at subsequent therapy) is defined as the time between the date of randomization and the date of first documented tumor progression, based on BICR assessments (per RECIST v1.1 criteria), or death due to any cause, whichever occurs first.

Subjects who die without a reported progression will be considered to have progressed on the date of their death. The following censoring rules will be applied for the primary definition of PFS:

- Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment.
- Subjects who did not have any on study tumor assessments and did not die will be censored on their date of randomization.
- Subjects who receive subsequent anti-cancer therapy prior to documented progression will be censored at the date of the last evaluable tumor assessment conducted on or prior to the date of initiation of the subsequent anti-cancer therapy.
- Subjects who did not have a documented progression and received subsequent anti-cancer therapy will be censored at the date of the last evaluable tumor assessment conducted on or prior to the initiation of the subsequent anti-cancer therapy.

Censoring rules for the primary definition of PFS (PFS truncated at subsequent therapy) are presented as follows and in Table 4.2.1.1-1.

Figure 4.2.1.1-1: PFS Primary Definition

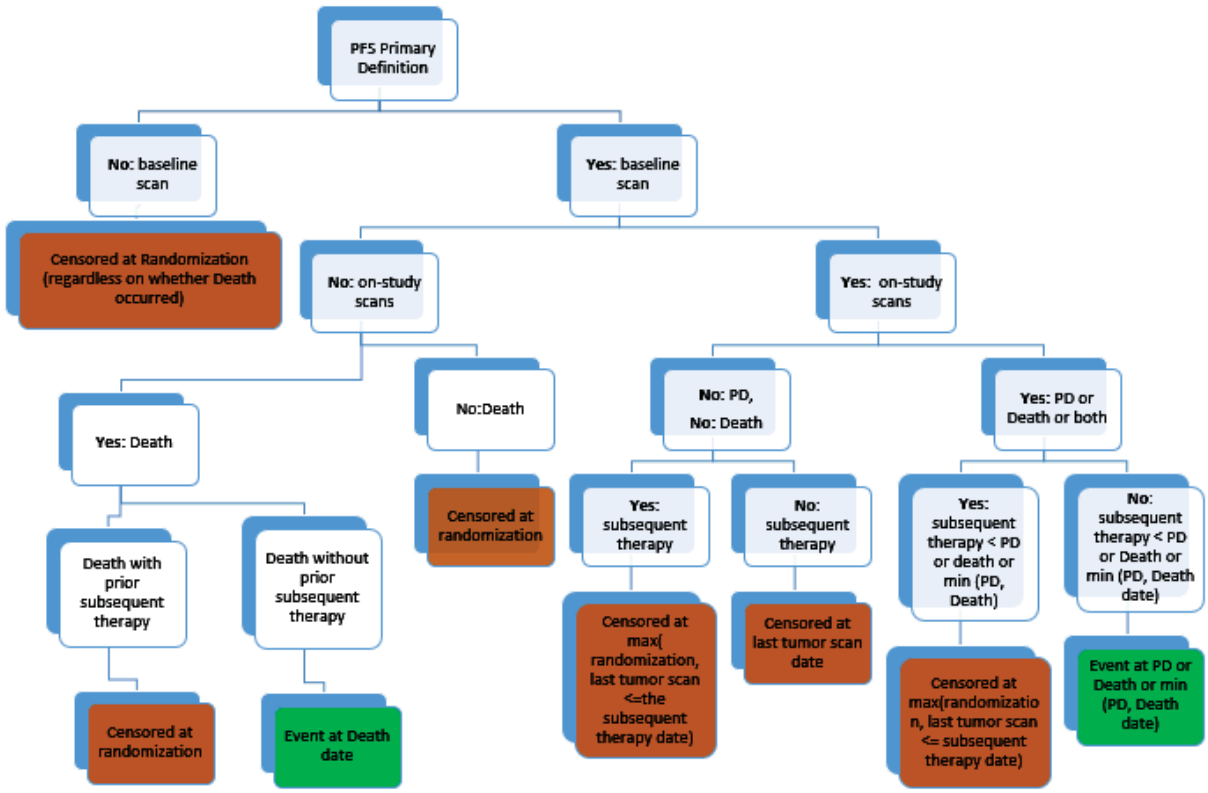


Table 4.2.1.1-1: Censoring Scheme used in Primary Definition of PFS

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments*	Date of randomization	Censored
No on study tumor assessments and no death*	Date of randomization	Censored
Subsequent anti-cancer therapy started without death or progression per RECIST v1.1 reported prior or on the same day	Date of last evaluable tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy	Censored
Documented progression per RECIST v1.1 and no new anti-cancer started before	Date of the first documented progression per RECIST v1.1 (excludes clinical progression)	Progressed
No progression and no death, and no new anti-cancer therapy started	Date of last evaluable tumor assessment	Censored
Death without progression per RECIST v1.1 and no new anti-cancer started before	Date of death	Progressed

* Tumor assessments and death if any, occurring after start of subsequent anti-cancer therapy are not considered.

4.2.1.2 Secondary Definition of Progression Free Survival (Irrespective of Subsequent Therapy)

The secondary definition of PFS (ITT definition) is defined as the time between the date of randomization and the date of first documented tumor progression, based on BICR assessments (per RECIST v1.1 criteria), or death due to any cause, whichever occurs first.

Subjects who die without a reported progression will be considered to have progressed on the date of their death. The following censoring rules will be applied for the secondary definition of PFS:

- Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment.
- Subjects who did not have any on study tumor assessments and did not die will be censored on their date of randomization.

Censoring rules for the secondary definition of PFS (ITT definition) are presented as follows and in Table 4.2.1.2-1.

Figure 4.2.1.2-1: PFS Secondary Definition

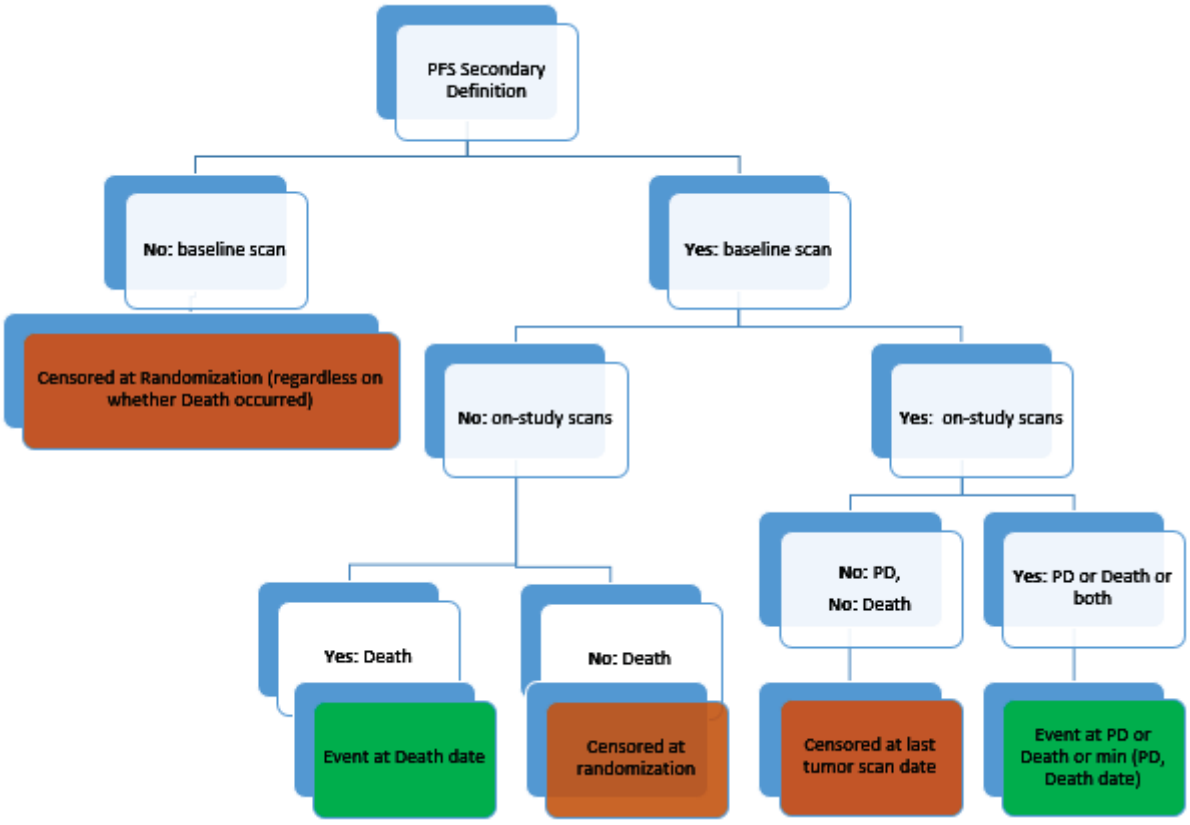


Table 4.2.1.2-1: Censoring Scheme for Secondary definition of PFS

Situation	Date of Progression of Censoring	Outcome
No baseline tumor assessment	Date of randomization	Censored
No on-study tumor assessments and no death	Date of randomization	Censored
Documented progression per RECIST v1.1	Date of first documented progression per RECIST v1.1 criteria (excludes clinical progression)	Progressed
No progression and no death	Date of last evaluable tumor assessment	Censored
Death without progression per RECIST v1.1	Date of death	Progressed

4.2.2 Objective Response Rate

Objective response rate (ORR) is defined as the number of treated subjects with a best overall response (BOR) of a complete response (CR) or partial response (PR) assessed by investigator per RECIST 1.1, divided by the number of treated subjects. Note that to achieve a best response of CR or PR, confirmation is required.

Best Overall Response (BOR)

BOR is defined as the best response designation, recorded between the first dosing date and the date of the initial objectively documented tumor progression assessed by investigator per RECIST 1.1, or the date of initiation of palliative local therapy or the date of initiation of subsequent anticancer therapy, whichever occurs first. For subjects without evidence of RECIST 1.1 progression or palliative local therapy or subsequent anticancer therapy, all available response designations will contribute to the BOR determination. For subjects who continue treatment beyond progression, the BOR will be determined based on response designations up to the time of initial RECIST 1.1-defined progression.

Radiographic tumor assessments will be conducted at Week 8 (± 7 days) and every 8 weeks (± 7 days) until up to 2 years or until disease progression (or until discontinuation of study therapy in patients receiving nivolumab beyond progression), lost to follow-up, or withdrawal of study consent. Assessment of partial assessment response (PR) and complete response (CR) must be confirmed at least 4 weeks following initial assessment.

4.2.3 Overall Survival (OS)

OS is defined as the time between the first dosing date and the date of death due to any cause. For subjects without documentation of death, OS will be censored on the last date the subject was known to be alive.

4.2.4 Duration of Response (DOR) and Time to Response (TTR)

Duration of Objective Response

Duration of Objective Response (DOR) is defined as the time between the date of first confirmed response (CR or PR) to the date of the first documented tumor progression (assessed by investigator per RECIST 1.1), or death due to any cause, whichever occurs first. Subjects who neither progress nor die will be censored on the date of their last evaluable tumor assessment. Subjects who started any subsequent anti-cancer therapy (including palliative local therapy) 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 (including palliative local therapy). DOR will be evaluated for responders (i.e. subjects with confirmed CR or PR) only.

Time to Response

Time to Response (TTR) is defined as the time from the date of the first dosing to the date of the first confirmed response (CR or PR). TTR will be evaluated for responders (i.e. subjects with a BOR of confirmed CR or PR) only.

[redacted]

5 SAMPLE SIZE AND POWER

Approximately 200 participants will be enrolled in order to treat up to 120 participants. This number of treated participants was chosen to provide descriptive analysis to estimate incidence rate of high-grade (Grades 3-4 or Grade 5), drug-related, select AEs and rate of immune-mediated AEs in all treated participants with nivolumab alternate dosing schedule. Overall, the safety profile of nivolumab monotherapy is manageable and generally consistent across completed and ongoing clinical trials with no MTD reached at any dose tested up to 10 mg/kg. Most AEs were low-grade (Grade 1 to 2) with relatively few related high-grade (Grades 3 to 4) AEs. Rates of high-grade (Grades 3-4 or Grade 5), drug-related, select AEs and rate of immune-mediated AEs by category observed in 2L NSCLC CheckMate 017 and 057 and 3L CheckMate 063 were low and <7%. Nivolumab monotherapy has been extensively studied in multiple tumor types, including melanoma, NSCLC, RCC, cHL, Head and Neck, and UC with body weight normalized dosing (mg/kg). PPK modelling predicted median and 95th percentile of exposures are maintained below those in 10 mg/kg every 2 weeks,[2] which was established as a safe and well-tolerable dose across multiple tumor types. There was no clinical meaningful relationship between nivolumab exposure or body weight and frequency or severity of AEs. Therefore, a 480 mg Q4W is expected to be safe and tolerable in those patients.

Table 5-1 shows the 95% Confidence Intervals for different AE rates for a sample size of 120 participants.

Table 5-1: 95% Confidence Intervals for different AE rates for a sample size of 120

Number of participants with AE (%)	Exact 95% CI around proportion
0/120 (0%)	0%-3.0%
1/120 (0.8%)	0%-4.6%
2/120 (1.7%)	0.2%-5.9%
3/120 (2.5%)	0.5%-7.1%
4/120 (3.3%)	0.9%-8.3%
5/120 (4.2%)	1.4%-9.5%
6/120 (5.0%)	1.9%-10.6%

With a sample size of 120, the chance of observing at least one participant with the event is greater than 80% for true probabilities of events higher than 1.3%.

- If true probability of event is 1%, the chance of observing at least 1 participant with event among 120 treated participant s is 70%.
- If true probability of event is 2%, the chance of observing at least 1 participant with event among 120 treated participant s is 91%.

Precision of secondary endpoint ORR, when sample size is 120, is provided in Table 5-2. If 24 responders are observed among the 120 treated participants (ORR =20%), the 2-sided exact 95% CI will be (13.3%, 28.3%). It is assumed that response rate would be similar to ORR observed in 2L NSCLC CheckMate017 and 057. With a target ORR = 19 %, this study has approximately 90% of power to exclude a 9% ORR (the null hypothesis) with a 0.05 two-sided significance level. The threshold response rate set at 9.0% is based on the response rate of docetaxel reported by Hanna et al[3]. as well as Japanese phase 2 ONO-4538-05 and 06 study.

Table 5-2: Precision of Secondary Endpoint of ORR

Number of responders (%)	Exact 95% CI around ORR
10/120 (8.3%)	4.1%-14.8%
11/120 (9.2)	4.7%-15.8%
18/120 (15%)	9.1%-22.7%
19/120 (15.8%)	9.8%-23.6%
20/120 (16.7%)	10.5%-24.6%
21/120 (17.5%)	11.2%-25.5%
22/120 (18.3%)	11.9%-26.4%
23/120 (19.2%)	12.6%-27.4%
24/120 (20.0%)	13.3%- 28.3%

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

6.1.1 Baseline Period

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

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

- Pre-treatment AEs will be defined as AEs with an onset date prior to but not including the day of the first dose of study treatment
- Baseline evaluations (laboratory tests, pulse oximetry and vital signs) will be defined as evaluations with a date on or prior to the day of first dose of study treatment

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

6.1.2 Post Baseline Period

On-treatment AEs will be defined as AEs with an onset date and time on or after the date and 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 event occurred within 30 days (or 100 days depending on analysis) (see Core Safety SAP), of the last dose of study treatment. No "subtracting rule" will be applied when an AE occurs both pre-treatment and post-treatment with the same preferred term and grade.

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, evaluation will be counted as on-treatment if it occurred within 30 days (or 100 days depending on analysis) of the last dose of study treatment.

6.2 Treatment Regimens

There is only one treatment regimen in this study:

- Nivo 480 mg Q4W

6.3 Populations for Analyses

- All enrolled subjects: All subjects who signed an informed consent form and were registered into the IRT system.
- All treated subjects: All enrolled subjects who received at least one dose of nivolumab.
- Response-Evaluable Subjects: All treated subjects with measurable disease at a baseline tumor assessment and at least one on-treatment tumor assessment.

[redacted]

- Interim Analysis Cohort: The first 56 treated subjects with an opportunity for minimum follow-up of 16 weeks. This dataset will be used for the first interim analyses of ORR/BOR and safety (in addition to safety analysis for all treated subjects). Subject's follow-up time is defined here as the time between first dosing date and database cutoff date.

[redacted]

7 STATISTICAL ANALYSES

7.1 General Methods

Unless otherwise noted, the following subsections describe tabulations of discrete variables, by the frequency and proportion of subjects falling into each category or summaries of continuous variables using descriptive statistics; ie, number of non-missing observations (n), mean, standard deviation (STD), median, minimum, maximum and quartiles.

Percentages given in these tables will be rounded and, therefore, may not always sum to 100%. . If a missing category is not being presented in the data display, only those subjects with non-missing values for the parameter being assessed are included in the percentage calculation.

Time to event distributions will be estimated using the Kaplan-Meier product limit method. This will be done for endpoints progression free survival, overall survival and duration of response

(note that time to response will be analyzed using summary statistics such as mean, SD, median, min, max). When appropriate, the median survival time along with associated 95% CIs will be constructed based on Brookmeyer and Crowley methodology[4] (using log-log transformed). Kaplan-Meier estimates of rates at fixed time points (e.g. OS at 12 months) will be presented along with 95% confidence intervals for those rates. The confidence interval for the rate at time t_0, $S(t_0)$, will be obtained by first computing the interval for $\log(-\log(S(t_0))$ and then back transforming.[5] (The methods specified above for computing the confidence intervals for median time to event and for survival rates are the default methods in SAS.[6])

Confidence intervals for binomial proportions will be derived using the Clopper-Pearson method.[7]

7.2 Study Conduct

7.2.1 Accrual

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

7.2.2 Relevant Protocol Deviations

The following programmable deviations will be considered as relevant protocol deviations and summarized in all treated subjects. Non-programmable relevant eligibility and on-treatment protocol deviations, as well as significant (both programmable and non-programmable) eligibility and on-treatment protocol deviations will be reported through [redacted] listings.

Eligibility:

- Subjects without measurable disease at baseline.
- Subject with baseline ECOG PS > 1

On-study:

- Subjects receiving anti-cancer therapy (chemotherapy, immunotherapy, standard or investigational agents for treatment of cancer, surgery (excluding palliative tumor resection), radiation therapy (excluding palliative tumor directed radiotherapy)) while on study therapy.

Listings will also be provided.

7.3 Study Population

Unless otherwise specified, analyses will be performed for all treated subjects.

7.3.1 Subject Disposition

The total number of subjects enrolled, treated or not treated will be presented along with the reason for not being treated. This analysis will be performed on the All Enrolled Subjects population.

Number of subjects who discontinued treatment as well as number of subjects not continuing in the study along with corresponding reason will also be tabulated. Reason for discontinuation will be derived from subject status CRF page.

A subject listing for all treated subjects will be provided showing the subject's first and last dosing date, off treatment date and reason for going off treatment.

7.3.2 Demographics and Other Baseline Characteristics

Descriptive statistics of the following baseline characteristics will be summarized:

- Age (descriptive statistics)
- Age category
  - <65,
  - >=65 and <75
  - >=75 and <85
  - >=85
  - >=75
  - >=65
- Gender
- Race
- Ethnicity
- Region
- Baseline weight (< 50 kg, ≥ 50 to < 70 kg, ≥ 70 to < 90 kg, ≥ 90 to < 110 kg, ≥ 110 kg)

7.3.3 Baseline Disease Characteristics

The following baseline disease characteristics will be summarized.

- Baseline ECOG PS (0, 1, not reported)
- Tobacco use (Never Smoker, Smoker, Unknown)

- Disease stage at initial diagnosis (Stage I, Stage II, Stage III, Stage IV)
- Cell type (adenocarcinoma, squamous cell carcinoma, large cell carcinoma, broncho-alveolar carcinoma, other)
- Disease status at initial diagnosis (locally advanced, locally recurrent, metastatic, locally recurrent and metastatic)
- Disease stage at study entry (Stage IIIB, Stage IV)
- Disease status at study entry (locally advanced, locally recurrent, metastatic, locally recurrent and metastatic)
- Baseline EGFR mutation status (positive, not detected, not reported)
- Sites of diseases (all lesions) per investigator
- Number of disease sites per subject (all lesions) per investigator
- Tumor burden: sum of the diameters of target lesions at baseline per investigator

[redacted]

- Baseline brain metastasis (Yes, No)
- Basline liver metastasis (Yes, No)

7.3.4 Medical History

General medical history will be listed by subject.

7.3.5 Prior Therapy

The following prior anti-cancer therapy will be summarized:

- Prior surgery related to current cancer (yes/no)
- Prior radiotherapy (yes/no) and type of radiotherapy
- Prior systemic cancer therapy (yes/no) and setting for current lung cancer condition (adjuvant, neo-adjuvant, multimodal and metastatic disease)
- Prior systemic cancer therapy classified by therapeutic class and generic name for current lung cancer condition.
- Best response to prior systemic cancer therapy (CR, PR, SD, PD, unable to determine, not applicable)

Medication will be reported using the generic name. A listing by subject will also be provided and will include details of site, type and dose of radiotherapy.

Prior/current non-study medication classified by anatomic and therapeutic classes will also be summarized.

7.3.6 Pre-Treatment AEs

Number and percentage of subjects with AEs related to non-small lung cancer will be summarized by CTC grade.

7.3.7 Baseline Examinations

Subjects with abnormal baseline physical examination will be tabulated by examination criteria.

7.4 Extent of Exposure

7.4.1 Administration of Study Therapy

The following parameters will be summarized (descriptive statistics):

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

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

Table 7.4.1-1: Study Therapy Parameter Definitions

	Nivolumab
Dosing schedule per protocol	480 mg every 4 weeks
Dose	*Dose (mg)* is defined as Total Dose administered in mg at each dosing date that is collected on the CRF.
Cumulative Dose	Cum Dose (mg) is the sum of the doses administered to a subject.
Relative dose intensity (%)	*[Cum dose (mg)/((* Last Nivolumab dose date - Nivolumab start dose date *+ 28) x 480 / 28)] x 100*
Duration of treatment	Last Nivolumab dose date - Nivolumab start dose date +1

In addition, 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. Median duration of treatment and associated 95% CI will be provided. Duration of combination treatment is the last dosing date of any drug component minus the first dosing date of any drug component plus one during the treatment phase.

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

7.4.2 Modifications of Study Therapy

7.4.2.1 Dose Delay

Nivolumab infusion may be delayed. A dose will be considered as actually delayed if the delay is exceeding 3 days (i.e., greater than or equal to 4 days from scheduled dosing date) for nivolumab. Reason for dose delay will be retrieved from CRF dosing pages.

Dose delay is defined as (duration of previous cycle in days - 28) for nivolumab. Dose delay will be divided into following categories: on-time, 4 - < 8 days, 8 - <15 days, 15 - <42 days, ≥ 42 days.

The following parameters will be summarized:

- Number of subjects with at least one dose delayed
- Number of dose delays per subject
- Length of delay
- Reason for delay

7.4.2.2 Infusion Modifications

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:

- Number of subjects with at least one infusion with 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 interruptions and number of infusions interrupted per subject

For treated subjects who experienced any dose interruption due to infusion reaction, number of infusion interrupted per subject (1, 2, 3, >=4) and descriptive statistics of doses received will be presented in a table. A listing of nivolumab infusions that were interrupted due to infusion reaction will accompany the table.

A by subject listing of study drug administered will be provided.

7.4.2.3 Dose Reduction

Dose reduction is not permitted for nivolumab.

7.4.3 Concomitant Medications

Concomitant medications, defined as medications other than nivolumab which are taken at any time on-treatment (i.e. on or after the first day of nivolumab and within 100 days following the last dose of nivolumab), will be coded using the WHO Drug Dictionary.

The following summary tables will be provided:

- Concomitant medications (subjects with any concomitant medication, subjects by medication class and generic term).

A by-subject listing will accompany the table.

7.5 Efficacy

CIs for efficacy endpoints will be at the two-sided 95% level. Point estimates and confidence intervals for efficacy variables will be rounded to the second decimal place.

7.5.1 The Analyses of ORR

7.5.1.1 ORR Analysis Methods

ORR assessed by investigator using RECIST 1.1 criteria will be summarized by a binomial response rate and its corresponding two-sided 95% exact CIs using Clopper-Pearson method.

BOR will be also summarized by response category.

ORR analysis will be repeated for response evaluable subjects (treated subjects with baseline and at least one on-study tumor assessment), if more than 10% treated subjects were not response evaluable.

There is no quantitative criterion for comparing the ORR results in this study versus historical trials because of the limited sample size.

7.5.1.2 Duration of Objective Response

DOR curves will be estimated using the KM product-limit method for responders (i.e. subjects with a BOR of CR or PR). Median DOR, corresponding two-sided 95% CI, and range will be reported. Proportion of subjects with duration of response at least 6 months will be estimated with corresponding two-sided 95% CI.

7.5.1.3 Time to Response

Time to objective response (TTR) will be summarized using descriptive summary statistics for the responders. Cumulative Response Rates will be tabulated for Month 2, 4, 6, 8, 10 and 12, and overall response rate will be provided.

7.5.1.4 Depth of Response

Depth of response will be summarized using descriptive summary statistics for the responders. Summary statistics for sum of diameters of target lesion and change from baseline at each visit and maximum tumor shrinkage from baseline will be provided.

The following subject-level graphics will also be provided:

- For the responders only, time courses of the following events of interest will be graphically displayed: tumor response, progression, last dose received, and death.
- For response evaluable subjects a waterfall plot showing the best reduction in target lesion will be produced.
- For response evaluable subjects, a plot of individual time course of tumor burden change will be produced.

7.5.1.5 Subset Analyses of ORR

To assess consistency of ORR, ORR assessed by investigator will be summarized for the following subsets for treated subjects:

- Age
  - i) <65,
  - ii) >=65 and <75
  - iii) >=75 and <85
  - iv) >=85
  - v) >=75
  - vi) >=65
- Gender (Male vs. Female)
- Race
- Region (North America vs. EU vs. Asia vs. ROW)
- ECOG performance status (0, 1)
- Disease stage at study entry (stage IIIB, stage IV)
- Tobacco use (Never Smoker, Smoker, Unknown)
- Baseline Histology (squamous, non-squamous)
- [redacted]
- Line of current therapy (2L, 3L and above).
- Baseline brain metastasis (Yes vs. No)
- Basline liver metastasis (Yes vs. No)
- Baseline weight (< 50 kg, ≥ 50 to < 70 kg, ≥ 70 to < 90 kg, ≥ 90 to < 110 kg, ≥ 110 kg)

ORR along with the exact 95% CI using Clopper-Pearson method will be displayed.

7.5.2 Progression Free Survival

Analysis of PFS will be conducted based on both the first definiton of PFS and the secondary definition of PFS.

7.5.2.1 Analysis of Porgression-Free Survival

Time to event distribution of PFS (assessed by investigator) will be estimated using Kaplan Meier techniques. Median PFS along with 95% CI will be constructed based on a log-log transformed CI for the survivor function. Rates at fixed time points (e.g. 6 months, depending on the minimum follow-up) will be derived from the Kaplan Meier estimate and corresponding confidence interval will be derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survivor function.

The source of PFS event (death vs. progression) will be summarized. The status of subjects who are censored in the PFS KM analysis will be tabulated using following categories:

- censored at the first dose date
- censored on date of last tumor assessment on-study or last assessment prior to subsequent anti-cancer therapy
  - On-study (on-treatment, in follow-up)
  - Off-study (lost to follow-up, withdrawn consent, other reason)

A by-subject listing for all treated subjects will be presented including PFS with censoring status and reason.

7.5.2.2 Current Status of Progression Free Survival Follow-up

Time from last tumor assessment to data cut-off in months will be summarized. Subjects who have a PFS event (using PFS definition accounting for assessment on/after subsequent therapy) will be considered as current for this analysis.

7.5.2.3 Subset Analyses of Progression Free Survival

To assess consistency of PFS among subgroups, the median PFS based on the Kaplan-Meier (KM) product-limit method along with two-sided 95% confidence intervals will be produced for the same subgroups as listed for ORR (Section 7.5.1.5). If a subset category has less than 5 subjects, median will not be computed/displayed.

7.5.2.4 Subsequent Therapy

The following information pertaining to subsequent therapies will be summarized:

Number and percentage of subjects receiving subsequent therapies including:

- Immunotherapy (anti-PD1 agents, anti-PD-L1 agents, anti-CTLA-4 agents and others) by drug name
- Other anti-cancer agents excluding all immunotherapy (approved and investigational) by drug name
- Palliative local therapy (including on-treatment)
- Surgery (limited to: tumor resection, curative; tumor resection, palliative, incisional biopsy; excisional biopy towards censoring for progression free survival)
- Radiotherapy
- Any combination of the above

A subject listing of follow-up therapy will be produced for subjects who had any subsequent therapy.

7.5.3 Overall Survival

7.5.3.1 Analysis of Overall Survival

Time to event distribution for OS will be estimated using Kaplan Meier technique. Median Survival time along with 95% CI will be constructed based on a log-log transformed CI for the survival function. Rates at fixed time points (e.g. 6 months, depending on the minimum follow-

up) will be derived from the Kaplan-Meier estimate and corresponding confidence interval will be derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survival function.

The status of subjects who are censored in the OS KM analysis will be tabulated using the following categories:

- On-study (on-treatment and not progressed, on-treatment pregressed, in follow-up)
- Off-study (lost to follow-up, withdrawn consent, etc.)

A by-subject listing will be presented including first and last dose date, whether the subject died, and if censored, the reason, event/censored date and OS duration.

7.5.3.2 Current Status of OS Follow-up

The extent of follow-up for survival defined as the time between start date of treatment and last known date alive (for subjects who are alive) or death date (for subjects who died) will be summarized descriptively (median, min, max) for all treated subjects. The current status of follow-up for survival, defined as the time between last OS contact (i.e., last known date alive or death date) and cutoff date (defined by last patient last visit date), will be summarized for all treated subjects. Subjects who died and subjects with last known date alive on or after data cut-off date will have zero value for currentness of follow-up. The currentness of follow-up will be categorized into the following categories: 0 day, 1 day-3 months, 3-6 months, 6-9 months, 9-12 months and ≥ 12 months.

[redacted]

7.5.4 Cross Study Comparison with Data from Studies CA209063, CA209017 and CA209057

Cross study comparison on efficacy endpoint ORR using case control analyses may be conducted, in which subjects from this study will be matched using propensity score matching analysis with subjects treated with nivolumab from studies CA209063, CA209017 and CA209057, based on relevant baseline covariates (eg. [redacted] histology, prior lines of therapy), and will be reported separately if conducted.

7.6 Safety

7.6.1 Rate of Drug-related Grade 3-5 Select AEs

In this study, the primary objective is to characterize the safety of nivolumab 480 mg IV over 30 minutes every 4 weeks. For purpose of the primary endpoint analysis, the drug-related Grade 3-5

select AE rate for all treated subjects will be reported with corresponding 95% CIs for the rate calculated using the Clopper-Pearson method.

Additional characterization of drug-related Grade 3-5 select AEs will be provided, including summaries by category/subcategory. Select AEs will be summarized for each category/subcategory using the 30-days safety window and repeated using the 100-day safety window (sensitivity analysis).

Select AEs analyses will include AEs with an onset date and time on or after the date and time of the first dose of nivolumab (or with an onset date on or after the day of first dose of nivolumab if time is not collected or is missing). For participants who are off study treatment, AEs will be included if an event occurred within a safety window of 30/100 days after the last dose of study treatment. No "subtracting rule" will be applied when an AE occurs both pre-treamtnet and post-treatment with the same preferred term and grade.

For more deatils in safety related analyses, refer to the Core Safety SAP.

7.6.2 Incidence of Infusion Reaction

Infusion reactions within 48 hours of dosing will be summarized for all treated subjects.

Standardised MedDRA Queries

Standardized MedDRA Queries (SMQs) are groupings of terms from one or more MedDRA System Organ Classes (SOCs) related to defined medical condition or area of interest. SMQ include terms that may relate to signs, symptoms, diagnoses, syndromes, physical findings, laboratory and other physiologic test data, etc. SMQs are developed by the council for international organizations of medical sciences and MedDRA maintenance and support services organization, are divided by two scopes:

- "Narrow" scope – specificity (cases highly likely to be condition of interest)
- "Broad" scope – sensitivity (all possible cases)

Only anaphylactic reaction (SMQ) will be summarized for each category, and repeated for narrow and broad scope respectively:

- Overall summary of any select Standardised MedDRA Queries (SMQs) by Preferred Term (PT)
- Overall summary of any select drug-related Standardised MedDRA Queries (SMQs) by PT

The analysis will be conducted using the 48 hours window of infusions. If only AE onset date information is available (not the time), AEs with onset date within 2 days of infusions (i.e., in the window of [infusion date, infusion date+2]) will be included.

7.6.3 Deaths

See Core Safety SAP.

7.6.4 Serious Adverse Events

See Core Safety SAP.

7.6.5 Adverse Events Leading to Discontinuation of Study Therapy

See Core Safety SAP.

7.6.6 Adverse Events Leading to Dose Delay of Study Therapy

See Core Safety SAP.

7.6.7 Adverse Events

See Core Safety SAP.

7.6.8 Adverse Events by Baseline Weight

All AEs, SAEs and AEs leading to discontinuation (any grade, grade 3-4, grade 5) will be summarized by baseline weight (< 50 kg, ≥ 50 to < 70 kg, ≥ 70 to < 90 kg, ≥ 90 to < 110 kg, ≥ 110 kg). Exact 95% CIs for events rates will be provided. Summaries by baseline weight will also be conducted for drug-related AEs, SAEs and AEs leading to discontinuation, Endocrine IMAEs, IMAEs where immune modulating medication was initiated (any grade, grade 3-4, grade 5).

7.6.9 Select Adverse Events

See Core Safety SAP.

7.6.10 Immune Modulating Medication

The percentage of treated subjects who received steroid concomitant medication for management of infusion reactions will be reported by medication class and generic term. Total duration of all steroid medications (excluding overlaps) given for infusion reaction management will be reported. The analysis will be conducted using the 30-day safety window.

See Core Safety SAP for other immune modulating medication analysis.

7.6.11 Multiple Events

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

- A table showing the number of subjects experiencing any unique select AE (0, 1, 2-3, >=4 events) by Category/PT
- A table showing the number of subjects experiencing any drug-related unique select AE (0, 1, 2-3, >=4 events) by Category/PT

In addition, the event count and exposure adjusted event rate will be provided for all treated subjects for following AEs:

- All AEs
- All serious AEs
- All select Standardised MedDRA Queries (SMQs) Broad/Narrow

- All drug-related select Standardised MedDRA Queries (SMQs) Broad/Narrow

The analyses will be conducted using the 30-day safety window except for SMQs, for which AEs with onset date within 2 days of infusions will be included.

A listing displaying the unique instances of all select 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 by category.

See Core Safety SAP for more details.

7.6.12 Other Events of Special Interest

See Core Safety SAP.

7.6.13 Immune-Mediated Adverse Events

See Core Safety SAP.

7.6.14 Clinical Laboratory Evaluations

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

7.6.14.1 Hematology

See Core Safety SAP.

7.6.14.2 Serum Chemistry

See Core Safety SAP.

[redacted]

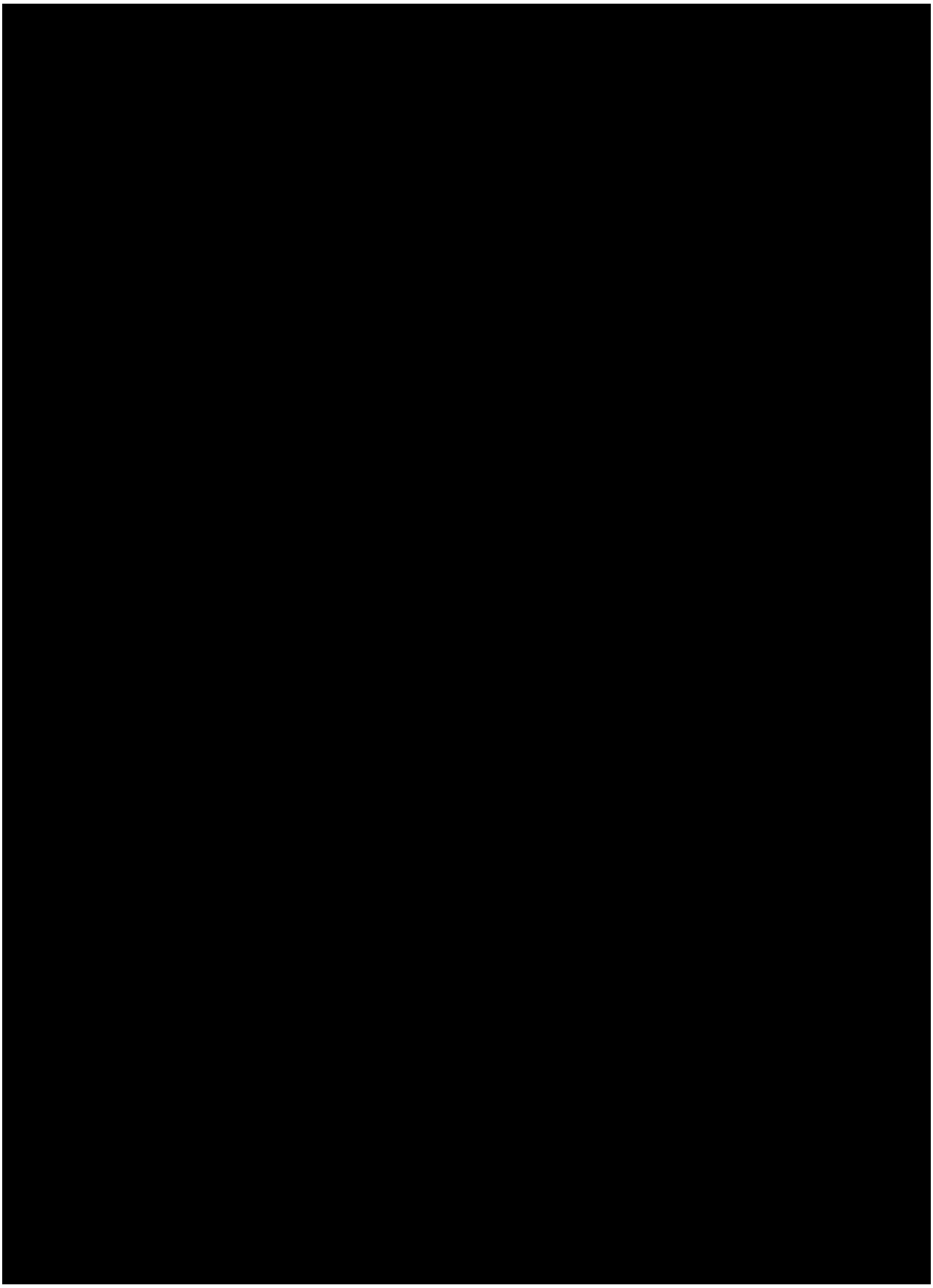
7.6.16 Vital Signs and Pulse Oximetry

See Core Safety SAP.

7.7 Pregnancy

See Core Safety SAP.

[redacted]



[redacted]

7.10 Other Analysis

A first interim analysis will be conducted when the first 56 treated subjects are followed for 16 weeks. ORR and BOR will be summarized for Interim Analysis Cohort (defined in section 6.3) using approaches specified in section 7.5.1.1. Key safety endpoints will be summarized for Interim Analysis Cohort and for all treated subjects in the locked database. A second interim analysis will be conducted when all treated subjects are followed for a minimum of 24 weeks. ORR, BOR, PFS and OS will be summarized for all treated subjects using approaches specified in section 7.5.1. Key safety endpoints will be summarized for all treated subjects in the locked database. IMAEs will be summarized using 100 days after the last dose of nivolumab window, other AE summaries will be based on 30 days after the last nivolumab dose window. Select Standardised MedDRA Queries (SMQs) Broad/Narrow summaries will be based on 2 days within nivolumab infusions.

8 CONVENTIONS

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

For missing and partial adverse event onset dates, imputation will be performed using the Adverse Event Domain Requirements Specification[8]. Missing and partial Non-Study Medication Domain dates will be imputed using the derivation algorithm described in 4.3.3 of BMS Non-Study Medication Domain Requirements Specification[9].

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 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 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 day

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

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day*.

- If the day and month are missing or a date is completely missing, it will be considered as missing.

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

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

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

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

Duration (e.g. time from first diagnosis to first dosing date, duration of response, and time to response) will be calculated as follows:

Duration = (Last date - first date + 1)

All statistical analyses will be carried out using [redacted] 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. [redacted] 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 version dated 21-May-2018
1.1		Added the second interim analysis in section 7.10. Added a by subject list of death. Added the efficacy subgroup analysis by baseline weight, brain metastasis and liver metastasis. Added the secondary definiton of PFS.

11 REFERENCES

1 Core Safety Statistical Analysis Plan for Multiple Indications, Nivolumab Program. BMS Document 930072588 5.0.

2 CA209003. Data on File.

3 Hanna N, Shepherd FA, Fossella FV, Pereira JR, Marinis F, Pawel J, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J ClinOncol. 2004;22(9):1589-97. Response Criteria

4 Brookmeyer, R. and Crowley, J. A confidence interval for the median survival time. Biometrics 38:29-41, 1982.

5 Kalbfleisch RL. The Statistical Analysis of Failure Time Data. Wiley-Interscience, 2002.

6 SAS/STAT 9.2 User's Guide, The Lifetest Procedure, Copyright 2008, SAS Institute Inc., Cary, NC, USA.

7 Clopper, CJ and Pearson, ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 26: 404-423, 1934.

8 Adverse Event Domain Requirements Specification. Bristol-Myers Squibb Co. PRI. Version 2.1. April 23, 2012.

9 Non-Study Medication Domain Requirements Specification. Bristol-Myers Squibb Co. PRI. Version 2.2 April 24, 2012.