Official Title of Study:

A STUDY OF NIVOLUMAB IN COMBINATION WITH IPILIMUMAB (PART 1); AND NIVOLUMAB PLUS IPILIMUMAB IN COMBINATION WITH CHEMOTHERAPY AS FIRST LINE THERAPY IN STAGE IV NON-SMALL CELL LUNG CANCER (NSCLC)

PROTOCOL(S) CA209568

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STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

A STUDY OF NIVOLUMAB IN COMBINATION WITH IPILIMUMAB (PART 1); AND NIVOLUMAB PLUS IPILIMUMAB IN COMBINATION WITH CHEMOTHERAPY AS FIRST LINE THERAPY IN STAGE IV NON-SMALL CELL LUNG CANCER (NSCLC)

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VERSION # 3.0

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Research Hypothesis:

Part 1:

In subjects with PD-L1 positive (membranous staining in (> = 1% tumor cells) and negative (membranous staining in < 1% tumor cells) stage IV NSCLC, the administration of nivolumab in combination with ipilimumab as first line treatment will lead to clinical benefit as demonstrated by a clinically meaningful objective response rate (ORR) and duration of response.

Part 2:

Nivolumab and ipilimumab combined with 2 cycles of standard of care chemotherapy are tolerable.

Schedule of Analyses:

The analysis of the primary endpoint of Part 1 will occur at least six months after the first treatment of the last patient from Part 1. It is anticipated that the analysis of the primary endpoint will take place approximately after 1.5 year (12 months enrollment and 6 months follow-up). Additional survival analysis may be conducted for up to 5 years beyond analysis of the primary endpoint. One interim analysis is planned at 3 month after the first treatment of the last patient in part 1.

For part 2, after total 28 (with at least 22 DLT evaluable subjects) have been treated and followed for at least 9 weeks, the analysis on dose-limiting toxicities (DLTs).will be done.

2 STUDY DESCRIPTION

2.1 Study Design

Adults (≥ 18 years) male and female subjects, with stage IV non-small cell lung cancer, previously untreated for advanced disease are eligible for enrollment, irrespectively of PD-L1 expression. Subjects will be assessed by PD-L1 expression, and categorized into 4 groups (PD-L1 positive, PD-L1 >= 50%, PD-L1 negative, and PD-L1 not quantifiable). PD-L1 status will be determined by Dako PD-L1 IHC 28-8 pharmDx test for immunohistochemical (IHC) staining of PD-L1 protein in the submitted tumor sample.

- PD-L1 positive (≥ 1% tumor cell membrane staining in a minimum of a hundred evaluable tumor cells)
- PD-L1 >= 50% (≥ 50% tumor cell membrane staining in a minimum of a hundred evaluable tumor cells). This is a subject set of subjects in all treated PD-L1 positive subjects.
- PD-L1 negative (< 1% tumor cell membrane staining in a minimum of a hundred evaluable tumor cells)
- PD-L1 not quantifiable (subjects with tumor biopsy specimens without quantifiable PD-L1 expression)

Throughout both parts of the study, subjects are to have tumor tissue sample available for PD-L1 IHC testing performed by the central lab during the screening period. In part 1, subjects can initiate therapy before the result of IHC testing. PD-L1 test will be used to track PD-L1 positive and PD-L1 negative treated subjects. Subjects in Part 2 may initiate therapy before IHC result.

Part 1 enrollment will end after at least 120 PD-L1 positive and 100 PD-L1 negative subjects are treated, whichever comes later (part 1 enrollment target was reached on Nov. 15 2016. Future enrollment will be in part 2 study).

In part 2 study, only receipt of suitable tissue by the central lab is required for treatment.

2.1.1 Part 1 study design

Part 1 is a phase II single arm clinical study of nivolumab (BMS-936558) in combination with ipilimumab as first line therapy in subjects with stage IV Non-Small Cell Lung Cancer (NSCLC).

Nivolumab is administered IV over 30 minutes at 3 mg/kg every 2 weeks combined with ipilimumab administered IV over 30 minutes at 1 mg/kg every 6 weeks until progression, unacceptable toxicity, or other reasons specified in the protocol. Treatment with nivolumab with ipilimumab will be given for a maximum of 2 years from the start of study treatment in the absence of disease progression or inacceptable toxicity.

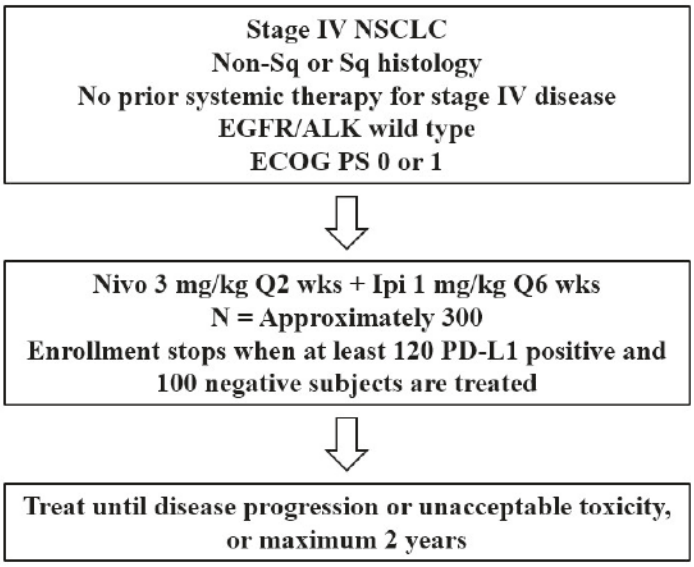
On-study tumor assessments will begin at 6 weeks post first dose date (+/-7 days) and be performed every 6 weeks (+/- 7 days) until week 48. After week 48, tumor assessments will be performed every 12 weeks (+/- 7 days) until blinded independent central review assessed

progression. Subjects received nivolumab plus ipilimumab beyond investigator-assessed progression must also continue tumor assessments until further progression at subsequent tumor assessment as indicated in the protocol.

Enrollment will end after at least 120 PD-L1 positive and 100 PD-L1 negative subjects are treated, whichever comes later. Assuming 35% screening failure rate and 50% all tested samples are PD-L1 positive, it is estimated that approximately 440 subjects will be enrolled in order to achieve 300 subjects treated which includes at least 120 PD-L1 positive and 100 PD-L1 negative treated subjects

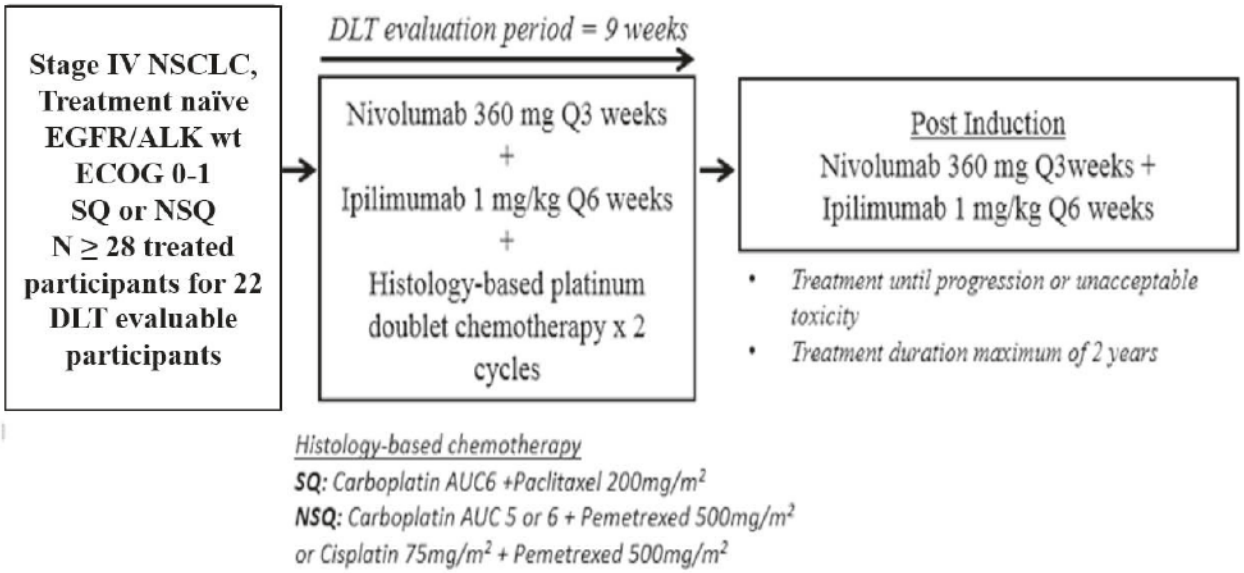
The study design schematic is presented in Figure 2.1.1-1

Figure 2.1.1-1: Part 1 Study Design Schematic



2.1.2 *Part 2 study design*

Figure 2.1.2-1: Part 2 Study Design Schematic



Part 2 will be conducted to evaluate safe dose level. Approximately 28 subjects will receive 2 cycles of induction chemotherapy and nivolumab plus ipilimumab. The starting dose of nivolumab is 360mg every 3 weeks and ipilimumab is 1 mg/kg every 6 weeks. .

Nivolumab will be administered with ipilimumab, plus 2 cycles of histology based platinum doublet chemotherapy as follows:

Squamous histology: Carboplatin AUC6 + Paclitaxel 200mg/m^2.

Non-squamous histology: Carboplatin AUC 5 or 6 + Pemetrexed 500mg/m^2 or Cisplatin 75mg/m^2 + Pemetrexed 500mg/m^2.

After above 2 cycles of induction treatment, nivolumab and ipilimumab will continue until disease progression or unacceptable toxicity, withdrawal of consent, or up a maximum of 2 years from the start of study treatment in the absence of disease progression or unacceptable toxicity.

On-study tumor assessments will begin at 6 weeks post first dose date (+/- 7 days) and be performed every 6 weeks (+/- 7 days) until week 48. After week 48, tumor assessments will be performed every 12 weeks (+/- 7 days) until blinded independent central review assessed progression or treatment discontinuation (whichever occurs later). Subjects receiving nivolumab plus ipilimumab beyond investigator assessed progression must also continue tumor assessments until further progression at subsequent tumor assessment as indicated in the protocol.

2.2 Treatment Assignment

Part 1:

After the subject's initial eligibility is established and informed consent has been obtained, the subject must be enrolled into the study by calling an interactive web response system (IWRS) to

obtain the subject number. Every subject that signs the informed consent form must be assigned a subject number in IWRS.

Subjects enrolled will be grouped according to PD-L1 status (positive or negative or not quantifiable defined in section 2.1). PD-L1 expression data will be transferred directly from analyzing lab to IWRS. IWRS will be used to track the enrollment number. The enrollment will end after at least 120 PD-L1 positive and 100 PD-L1 negative subjects are treated, whichever comes later.

The subject will be assigned a treatment vial number and will receive nivolumab at 3mg/kg IV every 2 weeks and Ipilimumab 1 mg/kg IV will be administered every 6 weeks following the administration of nivolumab.

Part 2:

In part 2 subjects meeting all eligibility criteria can initiate therapy before the result of PD-L1 IHC testing.

nivolumab will be administered with ipilimumab, plus 2 cycles of histology based platinum doublet chemotherapy as follows: Squamous histology: Carboplatin AUC6 + Paclitaxel 200mg/m2. Non-squamous histology: Carboplatin AUC 5 or 6 + Pemetrexed 500mg/m2 or Cisplatin 75mg/m2 + Pemetrexed 500mg/m2.

The exact procedures for using the IWRS will be detailed in the IWRS manual.

2.3 Blinding and Unblinding

Not applicable.

2.4 Protocol Amendments

Table 2.4-1: Protocol Amendments

Document	Date of Issue	Summary of Changes
Revised Protocol 06	02-Jan-2018	• Removed retreatment with nivolumab and ipilimumab for subsequent disease progression for up to 1 additional year and added justification for removing retreatment • Updated protocol with current contraceptive language • Updated protocol with current program treatment guidelines
Administrative Letter 02	09-Oct-2017	Remove EUDRACT number
Revised Protocol 05	28-Jul-2017	• Part 2 randomization phase was deleted from the study. Subsequently, the Part 2 randomization objectives, endpoints, analyses, and descriptions were removed. • Part 2 Safety Lead-in was modified and includes new [redacted] analyses, safety definitions, and

Table 2.4-1: Protocol Amendments

Document	Date of Issue	Summary of Changes
		additional language. • Additional research collection with residual sample storage was added.
Revised Protocol 04	13-Apr-2017	Incorporates amendment 04
Amendment 04	13-Apr-2017	• Amendment 04 changes the primary objective to progression-free survival and secondary objective to overall survival with subsequent changes to endpoints, analyses, and sample size. [redacted] • Chemotherapy dosing and modifications were updated. • Interim analyses were removed.
Revised Protocol 03	18-Jan-2017	Incorporates Amendment 03
Amendment 03	18-Jan-2017	[redacted] Updated tables 5.1-2 and 5.6.2.6-1[redacted] Inserted the dose modification instruction of Cisplatin in tables 4.5.3.2-1 and 4.5.3.4-1.The table was inadvertently modified in previously published version of the protocol. Corrected typographical errors throughout the protocol
Revised Protocol 02	07-Dec-2016	Incorporates Amendment 02
Amendment 02	07-Dec-2016	The study is expended by adding a randomized phase III part after completing enrollment to initial study. The treatment design is adding 2 cycles of chemotherapy as induction with nivolumab +ipilimumab, followed by nivolumab + ipilimumab until progression. A safety lead in of 28 patients will be conducted first to evaluate safe dose levels. After these subjects have been treated and followed for at least 9 weeks on study a decision will be made on the dose level for the randomization phase of part 2. 420 subjects will be randomized to treatment arm and control arm. The primary endpoint for part 2 is overall survival with nivolumab and ipilimumab plus chemotherapy vs. chemotherapy alone.
Administrative Letter 01	14-Oct-2016	Section 4.5.4.1 Criteria to Resume Nivolumab Dosing. Corrected a typographical error found in Revised Protocol v01 dated 21Sep2016, to the sixth bullet in regards to prednisone dosing. The ≥ sign was inadvertently used in lieu of the ≤ sign in front of the equivalent dose of prednisone 10mg/day.

Table 2.4-1: Protocol Amendments

Document	Date of Issue	Summary of Changes
Revised Protocol 01	21-Sep-2016	Incorporates Amendment 01
Amendment 01	21-Sep-2016	To increase sample size and some language adjustments on study objectives and stat analyses with added population of PD-L1>=50% and efficacy analyses in PD-L1 negative population.
Original Protocol	09-Dec-2015	Not applicable

2.5 Data Monitoring and Other External Committee

Not applicable.

3 OBJECTIVES

3.1 Primary

Part 1:

- To determine the objective response rate (ORR) in all treated PD-L1 positive (> = 1%) subjects by blinded independent central review per RECIST 1.1 in stage IV NSCLC subjects treated with nivolumab in combination with ipilimumab as first line therapy.
- To determine the ORR in all treated PD-L1 negative (< 1%) subjects by blinded independent central review per RECIST 1.1 in stage IV NSCLC subjects treated with nivolumab in combination with ipilimumab as first line therapy.

Part 2:

- To determine the incidence of DLT (dose limiting toxicity) during DLT evaluation period (within 9 weeks after first dose)
- To determine the safety and tolerability of nivolumab and ipilimumab combined with chemotherapy.

3.2 Secondary

Part 1:

- To assess ORR by blinded independent central review per RECIST 1.1 in all treated subjects treated with nivolumab in combination with ipilimumab as first line therapy.
- To assess progression free survival (PFS) based on blinded independent central review assessment.
- To assess overall survival.
- To assess ORR, PFS and OS by PD-L1 expression levels.
- To evaluate tumor mutation burden as a potential predictive biomarker of efficacy (such as ORR, PFS and OS) of nivolumab in combination with ipilimumab using DNA derived from tumor specimens.

Part 2:

- To evaluate ORR and PFS by investigator review using RECIST 1.1, and OS

[redacted]

4 ENDPOINTS

4.1 Primary Endpoint(s)

Part 1:

The primary objective will be measured by the primary endpoint of ORR (per RECIST v1.1 criteria, based on blinded independent central review) among the all treated PD-L1 positive and in PD-L1 negative subjects. Further characterization of the response will include duration of objective response and time to objective response.

Part 2:

The primary endpoint will be the incidence of DLT (dose limiting toxicity) during DLT evaluation period (within 9 weeks after first dose)and the safety and tolerability of nivolumab and ipilimumab combined with chemotherapy..

4.1.1 Objective Response Rate (ORR) in Part 1

4.1.1.1 Definition of ORR

ORR is defined as the number of subjects with a best overall response (BOR) of confirmed CR or PR divided by the number of treated subjects. BOR is defined as the best response designation, as determined by the blinded independent central review (by investigator in Part 2), recorded between the date of first dosing and the date of objectively documented progression

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 documented progression or palliative local therapy or subsequent anti-cancer 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 recorded up to the time of the initial RECIST 1.1-defined progression.

Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point of >= 4 weeks later.

4.1.1.2 Duration of Response

Duration of objective response (DOR) is defined as the time between the date of first confirmed response to the date of the first documented tumor progression (per RECIST 1.1) per BICR assessment, 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 as assessed by BICR.

4.1.1.3 Time to Response

Time to response is defined as the time, in months, from the date of first dosing to the first objective documentation of PR or better assessed per BICR. Time to response is restricted to the population of subjects who achieved a best response of PR or better assessed per BICR.

4.1.2 Dose limiting toxicities in Part 2

Dose limiting toxicities are defined as any of the items listed below which occur during the first 9 weeks.*

- Any Grade 2 drug-related uveitis or eye pain that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 2 drug-related pneumonitis or interstitial lung disease that does not resolve to dose delay and systemic steroids in 14 days (radiologic changes may take longer to resolve). The management algorithm for pneumonitis or pulmonary toxicity can be found in the appendix and in the current Investigator Brochure.[21]
- Any Grade 3 non-skin drug-related adverse event with the exception of laboratory abnormalities that cannot be alleviated (defined as returning to grade 1, radiologic changes may take longer to resolve) or controlled by appropriate care within 14 days (appropriate care being defined as treatment outlined in AE management algorithms in the investigators brochure).
- Any Grade 4 drug-related adverse event including laboratory abnormalities except Grade 4 leukopenia or neutropenia lasting < 14 days and asymptomatic amylase/lipase elevation
- Any of the following drug-related hepatic function laboratory abnormalities:

- AST or ALT >5-10x ULN for > 2 weeks
- AST or ALT > 10x ULN
- Total bilirubin > 5 x ULN
- Concurrent AST or ALT > 3x ULN and total bilirubin > 2x ULN
- Grade 3 thrombocytopenia associated with bleeding

*During the first 9 weeks: subjects should discontinue treatment if they experience any adverse event, laboratory abnormality or intercurrent illness (regardless of causality) which, in the opinion of the investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing. Such discontinuation, however, will not be considered a DLT unless it meets at least one of the DLT criteria defined above.

At the time of analysis, below safety-related analysis will be summarized to support to identify DLTs:

- Drug-related adverse events by worst CTC grade (any grade, grade 3-4, grade 5)
- Drug-related serious adverse events by worst CTC grade (any grade, grade 3-4, grade 5)
- Drug-related adverse events leading to discontinuation by worst CTC grade (any grade, grade 3-4, grade 5)
- Drug-related select adverse event by worst CTC grade (any grade, grade 3-4, grade 5)
- Drug-related severe adverse events leading to discontinuation by worst CTC grade (any grade, grade 3-4, grade 5)

4.1.3 Safety and tolerability

Safety will be analyzed through the incidence of deaths, adverse events, serious adverse events, adverse events leading to discontinuation, adverse events leading to dose delay, select adverse events and specific laboratory abnormalities (worst grade). Toxicities will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. See details in the Core Safety SAP.

4.2 Secondary Endpoint(s)

Secondary endpoints include:

Part 1:

- ORR by blinded independent central review per RECIST 1.1 in all treated subjects treated with nivolumab in combination with ipilimumab as first line therapy.
- Progression free survival (PFS) based on blinded independent central review assessment.
- Overall survival (OS).
- ORR, PFS and OS by PD-L1 expression levels.
- ORR, PFS, and OS by tumor mutation burden levels

Part 2:

- ORR, PFS, and OS

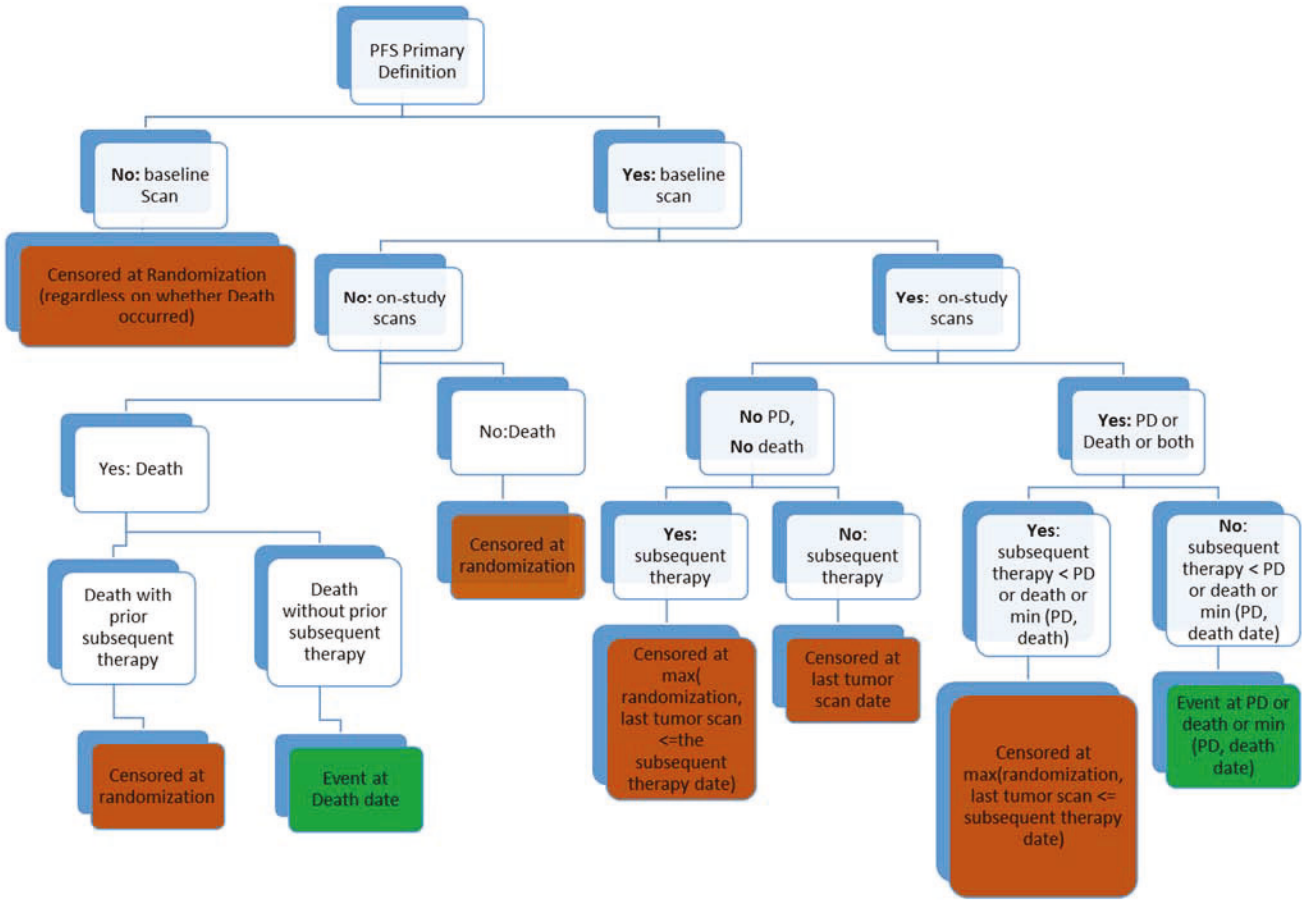
4.2.1 Progression Free Survival (PFS)

4.2.1.1 Primary Definition of PFS

PFS is defined as the time from the first dosing date to the date of the first documented tumor progression as determined by the blinded independent central review (per RECIST 1.1) in Part 1 and by investigator in Part 2, or death due to any cause, whichever occurs first.. Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. 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 he first dosing date. Subjects who had palliative local therapy or initiated anti-cancer therapy without a prior reported progression will be censored on the date of their last evaluable tumor assessment on or prior to the initiation of subsequent anti-cancer therapy or palliative local therapy. Tumor assessments will be conducted every 6 weeks (± 7 days) up to first 12 months (week 48), then every 12 weeks until disease progression or treatment discontinuation, whichever occurs later.

Further explanation for various censoring scenarios for the primary definition of PFS are presented in Figure 4.2.1.1-1.

Figure 4.2.1.1-1: Graphic display of PFS Primary Definition

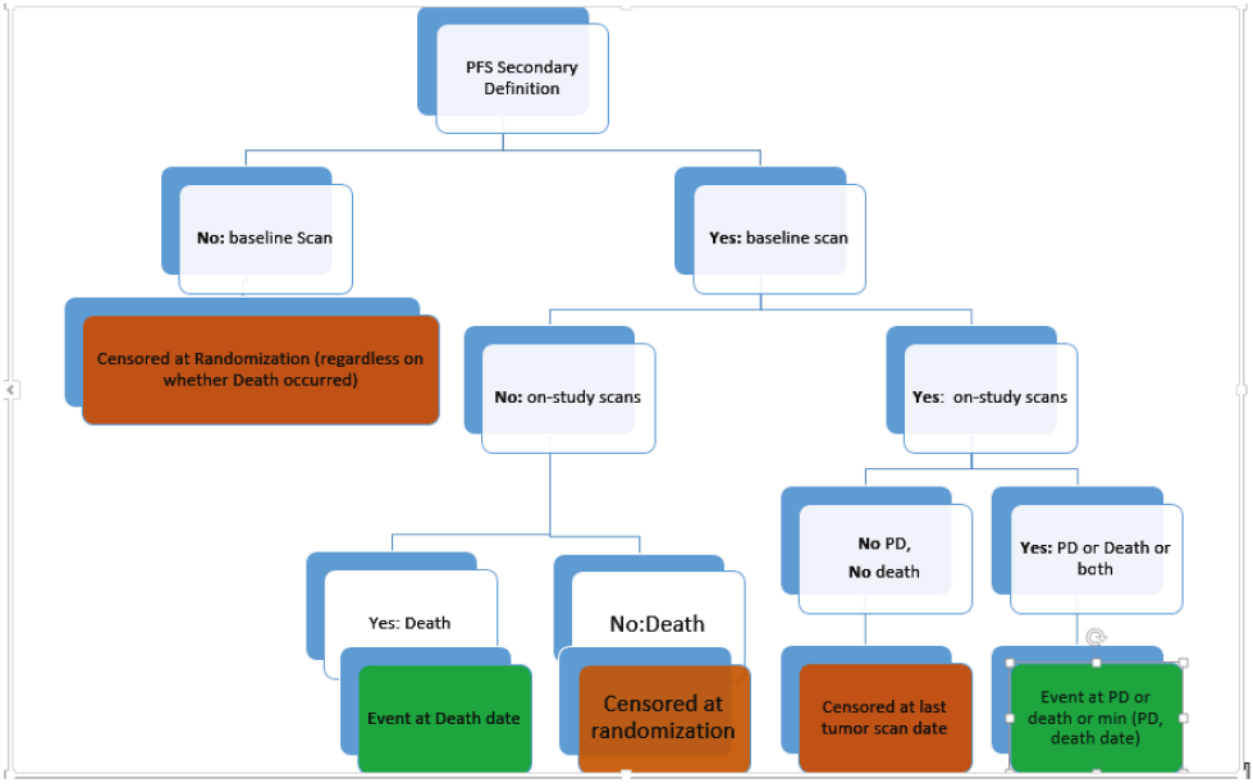


4.2.1.2 Secondary Definition of PFS

In the secondary definition of PFS, all tumor burden assessments including scans post the subjects' subsequent therapies will be taken into consideration. The secondary definition of PFS is defined as the time between the first dosing date and the first date of documented progression, as determined by the BICR (as per RECIST 1.1 criteria) in Part 1 and by investigator in Part 2, 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.

Further explanation for various censoring scenarios for the primary definition of PFS are presented in Figure 4.2.1.2-1.

Figure 4.2.1.2-1: Graphic Display of PFS Secondary Definition



4.2.2 Overall Survival (OS)

OS is defined as the time between the date of the first dosing date and the date of death due to any cause. A subject who has not died will be censored at last known date alive. Survival will be followed approximately every 3 months from Follow-Up Visit 2.

4.2.3 Tumor Mutational Burden (TMB)

TMB refers to the total number of nonsynonymous somatic mutations that exist within a tumor's genome. The pre-specified TMB cutpoint categorizing subjects as High TMB will be used for defining the subjects with High TMB (at or above the TMB cutpoint).

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, for all treated subjects.

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
- Baseline ECOG value is value recorded closest to (before or on) the first treatment date. If multiple records at same date then select the worst (highest value)

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

Post baseline period is further characterized into treatment, post-treatment follow-up.

Treatment period

- On-treatment AEs will be defined as AEs with an onset time after the time of the first dose of study treatment in cases where the time (onset time of event or evaluation time and dosing time) is collected. In cases where the time (onset time of event or evaluation time and dosing time) is missing or not collected, on-treatment AEs will be defined as AEs with an onset date on or after the day of first dose of study treatment. For subjects who are off study treatment, AEs will be included if event occurred within a safety window of 100 days after 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, evaluations will be counted as on-treatment if it occurred within a safety window of 100 of the last dose of study treatment.

Principal analysis of safety endpoints will be based on the assessments/evaluations collected during the treatment period. Late emergent drug-related AEs will be defined as drug-related AEs

with an onset data greater than 100 days after the last dose of study treatment in subjects off study treatment.

Post-Treatment Follow-up period

The post-treatment follow-up begins when the decision to discontinue a subject from all treatment is made per protocol. Efficacy analysis will include assessments collected during follow-up period per corresponding endpoint definitions.

6.2 Treatment Regimens

All subjects in part 1 are to be treated with nivolumab 3 mg/kg IV administered every 2 weeks and ipilimumab 1 mg/kg IV administered every 6 weeks following the administration of nivolumab.

In Part 2, approximately 28 subjects are planned to start with nivolumab 360mg every 3 weeks with ipilimumab 1 mg/kg every 6 weeks, plus 2 cycles of histology based platinum doublet chemotherapy as follows:

- Squamous histology: Carboplatin AUC 6 + Paclitaxel 200mg/m^2.
- Non-squamous histology: Carboplatin AUC 5 or 6 + Pemetrexed 500mg/m^2 or Cisplatin 75mg/m^2 + Pemetrexed 500mg/m^2

Nivolumab and ipilimumab will continue until disease progression or unacceptable toxicity, withdrawal of consent, or study closure.

6.3 Populations for Analyses

6.3.1 Populations for part 1 Analysis

- All enrolled subjects: all subjects who signed an informed consent form and were registered into the IWRS. This population will be used to for analysis of study conduct.
- All treated subjects: all subjects who received at least one dose of any study medication. This is the primary dataset for dosing, efficacy and safety.
  - All treated PD-L1 positive subjects: all treated subjects with PD-L1 membranous staining in ≥ 1% tumor cells.
  - All treated PD-L1 negative subjects: all treated subjects with PD-L1 membranous staining in < 1% tumor cells.
  - All Treated PD-L1 >= 50% subjects: all treated subjects with PD-L1 membranous staining in ≥ 50% tumor cells. This is a subject set of subjects in all treated PD-L1 positive subjects.
  - All treated PD-L1 not quantifiable subjects: all treated subjects with PD-L1 expression not quantifiable.
- All response evaluable subjects: treated subjects whose change in the sum of diameters of target lesions was assessed, i.e., target lesion measurements were made at baseline and at

least one on-study tumor assessment. This population is used for analysis of tumor burden changes over the time.

PD-L1 expression is defined as the percent of tumor cells membrane staining in a minimum of 100 evaluable tumor cells per Dako PD-L1 IHC 28-8 pharmDx test for immunohistochemical (IHC). This is referred to as quantifiable PD-L1 expression. PD-L1 not quantifiable is defined as subjects with no quantifiable PD-L1 expression at baseline which is likely due to insufficient tumor biopsy specimens for IHC staining and analysis.

If more than one tumor biopsy sample is available, PD-L1 expression is determined from the most recently collected pre-treatment sample with a quantifiable result. If all samples for a given subject are not quantifiable, then the PD-L1 expression will be considered not quantifiable. In part 1, statistical analysis using PD-L1 expression will be solely based on PD-L1 expression data from clinical database.

6.3.2 Populations for Part 2 in Analysis

- All enrolled subjects: all subjects who signed an informed consent form and were registered into the IWRS. This population will be used to for analysis of study conduct.
- All treated subjects: all subjects who received at least one dose of any study medication. This is the primary dataset for dosing, efficacy and safety.
- DLT evaluable subjects: all treated subjects excluding the subjects who did not complete the 9-week DLT evaluation period for reasons other than dose limiting toxicities, (ie, disease progression at or prior to first tumor assessment on study)

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 the mean, standard deviation, median, minimum and maximum values, grouped by:

- PD-L1 cohort:
    - PDL1 positive, PDL1 negative and all treated subjects for safety analysis.
    - PD-L1 >=50%, PD-L1 positive, PD-L1 negative, PD-L1 not quantifiable as well as the all treated population for all other analysis.

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 distribution will be estimated using Kaplan Meier techniques. 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 95% CI will be constructed based on Brookmeyer and Crowley methodology[15] (using log-log transformation for constructing the

confidence intervals). Rates at fixed time points (e.g., OS at 12 months) will be derived from the Kaplan Meier estimate along with their corresponding log-log transformed 95% confidence intervals[16].. Confidence intervals for binomial proportions will be derived using the Clopper-Pearson method [17].

7.2 Study Conduct

7.2.1 Accrual

The following will be presented on the enrolled population for part 1 and part 2 separately:

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

A by-subject listing of accrual will be produced.

7.2.2 Relevant Protocol Deviations

The following programmable deviations will be considered as relevant protocol deviations and be summarized. 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 ClinSIGHT listings.

At Entrance:

- Subjects with baseline ECOG performance status > 1
- Subjects without measurable disease at baseline as per investigator
- Subjects who received prior systemic anti-cancer treatment in the metastatic setting

On-study:

- Subjects receiving anti-cancer therapy (chemotherapy, immunotherapy, standard or investigational agents for treatment of cancer) while on study therapy.

A by subject listing will be produced.

7.3 Study Population

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 summary will be summarized in all enrolled subjects.

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.

7.3.2 Demographics and 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

7.3.3 Baseline Disease Characteristics

The following baseline disease characteristics will be summarized

- Baseline ECOG PS (0 vs.1 vs. 2 vs. 3 vs. 4 vs. not reported)
- Baseline weight
- Smoking status (Never, Former, Current, Unknown)
- Disease stage at study entry (Stage IV, Recurrent)
- Baseline Histology (Squamous cell carcinoma, Adenocarcinoma, Large cell carcinoma, Broncho-alveolar carcinoma, Other)
- Baseline EGFR mutation status (Positive, Not detected, Not reported)
- Baseline ALK translocation status (Positive, Not detected, Not reported)
- Baseline K-RAS mutation status (Positive, Not detected, Not reported)
- Baseline B-RAF mutation status (Positive, Not detected, Not reported)
- Baseline ROS1 mutation (Positive, Not detected, Not reported)
- Baseline RET mutation status (Positive, Not detected, Not reported)
- Baseline MET status (Positive, Negative, Unknown)
- Baseline HER-2 status (Positive, Negative, Unknown)
- Sites of diseases (all lesions) per BICR
- Number of disease sites per subject (all lesions) per BICR
- Sum of the diameters of target lesions at baseline per BICR

7.3.4 Medical History

General medical history will be listed by subject. Pre-treatment events will be summarized.

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, metastatic, neo-adjuvant)
- Prior systemic cancer therapy classified by therapeutic class and generic name for current lung cancer condition.

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

In part 1, the following parameters will be summarized (descriptive statistics):

- Number of doses received (nivolumab, ipilimumab and nivolumab after discontinuation of ipilimumab), summary statistics
- Cumulative dose (nivolumab and ipilimumab)
- Duration of treatment (nivolumab and ipilimumab, nivolumab, ipilimumab and nivolumab after discontinuation of ipilimumab)
- Relative dose intensity (%) using the following categories: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110% (nivolumab and ipilimumab)

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

Table 7.4.1-1: Part 1 Study Therapy Parameter Definitions- Nivolumab and Ipilimumab

	Nivolumab	Ipilimumab
Dosing schedule per protocol	3 mg/kg every 2 weeks	1 mg/kg every 6 weeks

Table 7.4.1-1: Part 1 Study Therapy Parameter Definitions- Nivolumab and Ipilimumab

	Nivolumab	Ipilimumab
Dose	*Dose (mg/kg)* is defined as Total Dose administered (mg)/Most recent weight (kg). Dose administered in mg at each dosing date and weight are collected on the CRF.	*Dose (mg/kg)* is defined as Total Dose administered (mg)/Most recent weight (kg). Dose administered in mg at each dosing date and weight are collected on the CRF.
Cumulative Dose	Cum Dose (mg/kg) is the sum of the doses administered to a subject.	Cum Dose (mg/kg) is the sum of the doses administered to a subject.
Relative dose intensity (%)	*[Cum dose (mg/kg)/((* Last Nivolumab dose date - Nivolumab start dose date *+ 14) x 3 / 14)] x 100*	*[Cum dose (mg/kg)/((* Last Ipilimumab dose date - Ipilimumab start dose date *+ 42) x 1 / 42)] x 100*
Duration of treatment	Last Nivolumab dose date - Nivolumab start dose date +1	Last Ipilimumab dose date - Ipilimumab start dose date +1

Table 7.4.1-2 to Table 7.4.1-6 summarizes the key parameters used to calculate dosing data in Part 2.

Table 7.4.1-2: Part 2 Study Therapy Parameter Definitions- Nivolumab and Ipilimumab

	Nivolumab	Ipilimumab
Dosing schedule per protocol	360 mg on day 1 every 3 weeks	1 mg/kg every 6 weeks
Dose	*Dose (mg)* is defined as Total Dose administered in mg at each dosing date is collected on the CRF.	*Dose (mg/kg)* is defined as Total Dose administered (mg)/Most recent weight (kg). Dose administered in mg at each dosing date and weight are collected on the CRF.
Cumulative Dose	*Cum dose (mg) is* sum of the doses (mg) administered to a subject.	Cum Dose (mg/kg) is the sum of the doses administered to a subject.
Relative dose intensity (%)	Cum dose (mg)/[(Last Nivolumab dose date - Nivolumab start dose date + 21) x 360/21] x 100	*[Cum dose (mg/kg)/((* Last Ipilimumab dose date - Ipilimumab start dose date *+ 42) x 1 / 42)] x 100*
Duration of treatment (overall)	Last Nivolumab dose date - Nivolumab start dose date +1	Last Ipilimumab dose date - Ipilimumab start dose date +1

Table 7.4.1-3: Part 2 Study Therapy Parameter Definitions- Paclitaxel/Carboplatin (Squamous)

	Paclitaxel	Carboplatin
Dosing schedule per protocol	200 mg/ m^2every 3 weeks	AUC 6 every 3 weeks

Table 7.4.1-3: Part 2 Study Therapy Parameter Definitions- Paclitaxel/Carboplatin (Squamous)

	Paclitaxel	Carboplatin
Dose	*Dose (mg/m²)* is defined as Total Dose administered in mg at each dosing date is collected on the CRF and BSA is derived from most recent weight and baseline height also collected on the CRF.	*Dose (AUC)* is defined as Total Dose administered (mg)/(creatinine clearance +25). Dose administered in mg at each dosing date is collected on the CRF and creatinine clearance derived from the CRF data.
Cumulative Dose	*Cum dose (mg/m²) is* sum of the doses (mg/m²) administered to a subject.	*Cum dose (AUC) is* sum of the doses (AUC) administered to a subject.
Relative dose intensity (%)	Cum dose (mg/m²)/[(Last paclitaxel dose date - paclitaxel Start dose date + 21) x 500/21] x 100	Cum dose (AUC)/[(Last dose date of Carbo - Start dose date of Carbo + 21) x 6/21] x 100
Duration of treatment	Last dose date - Start dose date +1	Last dose date - Start dose date +1

Table 7.4.1-4: Part 2 Study Therapy Parameter Definitions- Pemetrexed/Carboplatin (Non-squamous)

	Pemetrexed	Carboplatin
Dosing schedule per protocol	500mg/m² every 3 weeks	AUC 5 on day 1 of every 3 week cycle
Dose	*Dose (mg/m²)* is defined as Total Dose administered in mg at each dosing date is collected on the CRF and BSA is derived from most recent weight and baseline height also collected on the CRF.	*Dose (AUC)* is defined as Total Dose administered (mg)/(creatinine clearance +25). Dose administered in mg at each dosing date is collected on the CRF and creatinine clearance derived from the CRF data.
Cumulative Dose	*Cum dose (mg/m²) is* sum of the doses (mg/m²) administered to a subject.	*Cum dose (AUC) is* sum of the doses (AUC) administered to a subject.
Relative dose intensity (%)	Cum dose (mg/m²)/[(Last Pemetrexed dose date - Pemetrexed Start dose date + 21) x 500/21] x 100	Cum dose (AUC)/[(Last dose date of Carbo - Start dose date of Carbo + 21) x 5/21] x 100
Duration of treatment	Last dose date - Start dose date +1	Last dose date - Start dose date +1

Table 7.4.1-5: Part 2 Study Therapy Parameter Definitions- Pemetrexed/Carboplatin (Non-squamous)

	Pemetrexed	Carboplatin

Table 7.4.1-5: Part 2 Study Therapy Parameter Definitions-Pemetrexed/Carboplatin (Non-squamous)

	Pemetrexed	Carboplatin
Dosing schedule per protocol	500mg/m² every 3 weeks	AUC 6 every 3 weeks
Dose	*Dose (mg/m²)* is defined as Total Dose administered in mg at each dosing date is collected on the CRF and BSA is derived from most recent weight and baseline height also collected on the CRF.	*Dose (AUC)* is defined as Total Dose administered (mg)/(creatinine clearance +25). Dose administered in mg at each dosing date is collected on the CRF and creatinine clearance derived from the CRF data.
Cumulative Dose	*Cum dose (mg/m²) is* sum of the doses (mg/m²) administered to a subject.	*Cum dose (AUC) is* sum of the doses (AUC) administered to a subject.
Relative dose intensity (%)	Cum dose (mg/m²)/[(Last Pemetrexed dose date - Pemetrexed Start dose date + 21) x 500/21] x 100	Cum dose (AUC)/[(Last dose date of Carbo - Start dose date of Carbo + 21) x 6/21] x 100
Duration of treatment	Last dose date - Start dose date +1	Last dose date - Start dose date +1

Table 7.4.1-6: Part 2 Study Therapy Parameter Definitions-Pemetrexed/Cisplatin (Non-squamous)

	Pemetrexed	Cisplatin
Dosing schedule per protocol	500 mg/ m² every 3 weeks	75mg/ m² every 3 weeks
Dose	*Dose (mg/m²)* is defined as Total Dose administered (mg)/Most recent BSA. Dose administered in mg at each dosing date is collected on the CRF and BSA is derived from most recent weight and baseline height also collected on the CRF.	*Dose (mg/m²)* is defined as Total Dose administered (mg)/Most recent BSA. Dose administered in mg at each dosing date is collected on the CRF and BSA is derived from most recent weight and baseline height also collected on the CRF.
Cumulative Dose	*Cum dose (mg/m²) is* sum of the doses (mg/m²) administered to a subject.	*Cum dose (mg/m²) is* sum of the doses (mg/m²) administered to a subject.
Relative dose intensity (%)	Cum dose (mg/m²)/[(Last Pemetrexed dose date - Pemetrexed Start dose date + 21) x 500/21] x 100	Cum dose (mg/m²)/[(Last Cisplatin dose date - Cisplatin Start dose date + 21) x 75/21] x 100
Duration of treatment	Last dose date - Start dose date +1	Last dose date - Start dose date +1

Where the creatinine clearance will be calculated using Cockroft-Gault formula, defined as:

$$\text{CrCL(ml/min)} = \frac{(140 - \text{age (in years)}) * \text{weight (in kg)}}{72 * \text{serumcreatinine (in mg/dL)}}$$

for males and

$$\text{CrCL(ml/min)} = \frac{(140 - \text{age (in years)}) * \text{weight (in kg)}}{72 * \text{serumcreatinine (in mg/dL)}} * 0.85$$

for females. The most recent weight will be used. If the computed creatinine clearance is more than 125 ml/min, then the creatinine clearance value should be capped at 125ml/min for dose exposure computations

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: weight, number of doses, cumulative dose, relative dose intensity, duration of treatment, and reason for dose change for each drug. A batch listing number will be also provided.

7.4.2 Modification of Study Therapy

7.4.2.1 Dose Delay

Each study medication 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 study medication. All study drugs must be delayed until treatment can resume. Reason for dose delay will be retrieved from CRF dosing pages.

Dose delay is defined as (duration of previous cycle in days - 14) for nivolumab in part 1, (duration of previous cycle in days - 42) for ipilimumaband (duration of previous cycle in days - 21) for all other drugs. Dose delays 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 by each study drug:

- 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

Each study drug 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 study drug:

- 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

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

7.4.2.3 Dose Reductions

There will be no dose reductions of nivolumab and ipilimumab allowed. Dose of platinum doublet chemotherapy in Part 2 may be modified for toxicity. Dose levels of platinum doublet chemotherapy are defined in the protocol as follows:

Table 7.4.2.3-1: Dose Modifications of Chemotherapeutic Agents

Dose Level	Carboplatin	Pemetrexed	Paclitaxel	Cisplatin
Starting dose	AUC 6 or 5 with pemetrexed/ or AUC 6 with Paclitaxel	500 mg/m²	200 mg/m²	75 mg/m²
First dose reduction	AUC 5 if starting dose is AUC 6 or 4 if starting dose if AUC 5 with pemetrexed/ or AUC 5 with Paclitaxel	375 mg/m²	150 mg/m²	56 mg/m²
Second dose reduction	AUC 4 if starting dose is AUC 6 or 3 if starting dose is AUC 5 with pemetrexed/ or AUC 4 with Paclitaxel	250 mg/m²	100 mg/m²	38 mg/m²
Third dose reduction	Discontinue	Discontinue	Discontinue	Discontinue

For any cycle, it will be defined as a dose reduction if the observed dose level (based on calculated administered dose) is below protocol specified dose level. Dose ranges for dose levels of platinum doublet chemotherapy are defined in Table 7.4.2.3-2.

Table 7.4.2.3-2: Calculated Dose Ranges and Related Dose Levels

Dose Level	Carboplatin (AUC)	Pemetrexed	Paclitaxel	Cisplatin
Level 0	With pemetrexed: ≥5.5 (start of AUC 6) or ≥4.5 (start of AUC 5) With Paclitaxel: ≥5.5	≥437.5	≥175	≥65.5
Level 1	With pemetrexed: <5.5 and ≥4.5 (start of AUC 6) or <4.5 and ≥3.5 (start of AUC 5) With Paclitaxel: <5.5 and ≥4.5	<437.5 and ≥312.5	<175 and ≥125	<65.5 and ≥47
Level 2	With pemetrexed: <4.5 (start of AUC 6) or <3.5 (start of AUC 5) With Paclitaxel: <4.5	<312.5	<125	<47

Number and percentage of subjects with at least one dose reduction and reason of the dose reduction, number and percentage of subjects with a dose reduction to dose level -1, number and percentage of subjects with a dose reduction to dose level -2 will be summarized for subjects in Part 2. The reason for dose reduction as reported by the investigator will be tabulated for all instances of dose reduction based on the Dose Change CRF page. A category 'Unknown' will be defined for all reductions with no reason reported by the investigator.

7.4.3 Partial Discontinuation of ipilimumab

Subjects may discontinue ipilimumab and continue to receive nivolumab alone (ie, partial discontinuation). Continuation of ipilimumab after discontinuation of nivolumab is not allowed on study.

The following will be summarized

- Number and percentage of subjects who had partial discontinuation of ipilimumab.
- Reason for partial discontinuation.

Reason for partial discontinuation will be retrieved from dosing CRF pages.

[redacted]

7.5 Efficacy

Unless otherwise specified, the efficacy data will be presented by PD-L1 cohort as well as all treated subjects. Supporting listings will be provided for each endpoint. Analyses will be performed for Part 1 and Part 2 separately.

7.5.1 Statistical Methods for Primary Endpoint of ORR (BICR-assessed) in Part 1

7.5.1.1 ORR analysis methods

ORR (based on blinded independent central review (BICR) assessments using RECIST 1.1 criteria with requirement for response confirmation) 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.

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 per BICR assessment). 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 Week 6, Month 3, 6, 9, and 12, and overall response rate will be provided.

7.5.1.4 Depth of Response

Depth of response based on BICR measurements will be summarized using descriptive summary statistics for the responders. Summary statistics for sum of diameters of target lesion and change from baseline per BICR 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 based on BICR assessment will be produced.
- For response evaluable subjects, a plot of individual time course of tumor burden change per BICR will be produced.

7.5.1.5 ORR Subgroup Analyses

To assess consistency of ORR, BICR-assessed ORR will be summarized for the following subsets within PD-L1+, PD-L1-, and all treated population

- Age
  - <65,
  - >=65 and <75
  - >=75 and <85
  - >=85
  - >=75
  - >=65
- Gender (Male, Female)
- Race
- Baseline ECOG (0 vs. 1 vs. >1)
- Smoking status (Never, Former, Current, Unknown)
- Baseline Histology (Squamous, Non-Squamous)

7.5.2 Statistical Methods for Secondary Endpoints

7.5.2.1 Progression Free Survival based on BICR

Time to event distribution of PFS (based on BICR assessments) 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, withdrew consent, other reason).

Consistency of PFS in Subsets

To assess consistency of PFS based on BICR assessment 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 the primary endpoint (Section 7.5.1) within PD-L1+, PD-L1-, and all treated population. If a subset category has less than 5 subjects, median will not be computed/displayed.

Current Status of PFS 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.

7.5.2.2 Overall Survival

Time to event distribution for OS will be estimated using Kaplan Meier techniques. Median OS 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 status of subjects who are censored in the OS KM analysis will be tabulated 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.)

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.

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 biopsy towards censoring for progression free survival per primary definition)
- Radiotherapy
- Any combination of the above

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

7.5.2.3 Tumor mutation burden and their association with ORR, PFS, and OS

The pre-specified TMB cutpoint categorizing subjects as High TMB will be used for defining the subjects with High TMB (at or above the TMB cutpoint).

ORR by TMB

ORR as per BICR assessment among all treated TMB evaluable subjects, and subjects with high TMB with estimating ORR and corresponding 95% exact CI using Clopper-Pearson method. The number and percentage of subjects in each category of best overall response per BICR (confirmed complete response [CR], confirmed partial response [PR]], stable disease [SD], progressive disease [PD], or unable to determine [UD]) according to the BICR will be presented.

PFS by TMB

PFS among all treated TMB evaluable subjects, and subjects with high TMB will be conducted. PFS curve will be estimated using the Kaplan-Meier product limit method. Two-sided, 95% confidence intervals for median PFS will be computed by Brookmeyer and Crowley method.

OS by TMB

OS among all treated TMB evaluable subjects, and subjects with high TMB will be conducted. OS curve will be estimated using the Kaplan-Meier product limit method. Two-sided, 95% confidence intervals for median OS will be computed by Brookmeyer and Crowley method.

More details of the analysis on TMB are described in section 7.7.2

7.5.3 Statistical Methods for Efficacy by Investigator Assessment

7.5.3.1 ORR, by investigator assessment

ORR per investigator's assessment using the primary definition 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.

To assess concordance between BICR and investigator assessments, BOR will be cross-tabulated by assessment type (Investigator vs. BICR). Concordance Rate of Responders will be computed as the frequency with which INV and BICR agree on classification of a subject as responder/non responder as a proportion of the total treated subjects.

The duration of response and time to response per investigator will be summarized similarly for subjects who achieve confirmed PR or CR using the primary definition.

7.5.3.2 PFS by investigator assessment

PFS based on investigator assessments will be analyzed similarly using primary definition:

- KM curves of PFS will be generated;
- Median and two sided 95% CI will be computed.

7.5.3.3 Efficacy Analyses Beyond Progression

A subject listing will be provided for subjects with treatment beyond investigator assessed progression including number of doses/duration received beyond progression.

7.6 Safety

Whenever appropriate, this section refers to the nivolumab Core Safety SAP for details on statistical analyses.

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.

Additionally, the following summary of AEs leading to partial discontinuation of study therapy will be presented.

- Overall summary of AEs leading to partial discontinuation by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by SOC/PT
- Overall summary of drug-related AEs leading to partial discontinuation by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.

- Overall summary of SAEs, drug-related SAEs leading to partial discontinuation presented by SOC/PT.

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

7.6.4 Adverse Events Leading to Dose Modification

See Core Safety SAP.

7.6.5 Adverse Events

See Core Safety SAP.

7.6.6 Select Adverse Events

See Core Safety SAP.

7.6.7 Immune modulating medication

See Core Safety SAP.

7.6.8 Multiple Events

See Core Safety SAP.

7.6.9 Immune Mediated Adverse Events

See Core safety SAP

7.6.10 Laboratory Parameters

See Core Safety SAP.

7.6.11 Vital Signs and Pulse Oximetry

See Core Safety SAP.

7.6.12 Pregnancy

See Core Safety SAP.

7.6.13 Clinical Safety Program (CSP)

CSP CRF pages will be used for narratives generation and IMAEs evaluation. No summary display will be provided.

7.6.15 Adverse Events By Subgroup

See Core Safety SAP.

[redacted]

[redacted]

[redacted]

[redacted]

7.10 Other Analysis

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[18].
- 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[19].

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 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. 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

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 case of 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 (eg, time from first diagnosis of NSCLC to first dosing date, duration response, and time to response) will be calculated as follows:

Duration = (Last date - first date + 1)

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 describe in this SAP will be included in the final Clinical Study Report. Refer to the Data Presentation Plan for mock-ups of all tables and listings.

10 DOCUMENT HISTORY

Table 10-1: Document History

Version Number	[redacted]	Description
1.0	[redacted]	Initial version **1-May-2017**
2.0	[redacted]	Remove Part 2 randomization phase per protocol amendment 05.
3.0	[redacted]	Removed retreatment with nivolumab and ipilimumab per protocl amendment 06 and aligned the language with the protocol