Official Title of Study:

A Master Protocol of Phase 1/2 Studies of Nivolumab in Advanced NSCLC Using Nivolumab as Maintenance after Induction Chemotherapy or as First-line Treatment Alone or in Combination with Standard of Care Therapies

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STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

SUSTAIN: A MASTER PROTOCOL OF PHASE 1/2 STUDIES OF NIVOLUMAB IN ADVANCED NSCLC USING NIVOLUMAB AS MAINTENANCE AFTER INDUCTION CHEMOTHERAPY OR AS FIRST-LINE TREATMENT ALONE OR IN COMBINATION WITH STANDARD OF CARE THERAPIES

PROTOCOLS CA209370

VERSION # 2.0

DOCUMENT HISTORY

Document	Date of Issue	Summary of Changes
Version 1	13-Jun-2016	Original Issue
Version 2	25-Jul-2018	Changes for Revised Protocol 05 Amendment 04 dated 26MAR2018

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

[redacted]

2 STUDY DESCRIPTION

This is an open-label, Phase 1/2, Master Protocol (revised protocol 05), containing 5 sub-studies (sub-protocols), that will each enroll a unique patient population. Subjects with recurrent locally advanced

or Stage 4 SQ or NSQ NSCLC, with an ECOG PS of 0-2, will receive either first-line or maintenance therapy with nivolumab as a single-agent or in combination with SOC therapies. Subjects will be assigned to one of the following treatment groups based on histology, ECOG PS, and mutation status:

- Group A subjects with NSQ NSCLC and a PS 0-1 will be randomized (1:1:1) to receive single-agent nivolumab, single-agent pemetrexed or bevacizumab, or the combination of nivolumab and pemetrexed or bevacizumab, as maintenance therapy following first-line treatment with Investigator's Choice chemotherapy. The primary objectives of Group A are to compare PFS and OS of single-agent bevacizumab versus single-agent nivolumab, or the combination of nivolumab and bevacizumab, or single-agent pemetrexed versus single-agent nivolumab, or the combination of nivolumab and pemetrexed.; comparisons of DOR and ORR are the secondary objectives.
- Group B subjects with SQ NSCLC and a PS 0-1 will be randomized (1:1) to receive either single-agent nivolumab or best supportive care (BSC) as maintenance following first-line treatment with Investigator's Choice chemotherapy. The primary objectives of Group B are to compare PFS and OS of single-agent nivolumab versus BSC; comparisons of DOR and ORR are the secondary objectives.
- Group C subjects with NSCLC of NSQ or SQ histology with PS 2 will be randomized (1:1) to receive either Investigator's Choice chemotherapy or single-agent nivolumab as first-line treatment. The primary objectives of Group C are to compare PFS and OS of single-agent nivolumab versus Investigator's Choice chemotherapy. The secondary objectives are the comparisons of DOR and ORR.
- Group D subjects with NSCLC histology and EGFR mutation, and a PS 0-2 will be randomized (1:1) to first-line treatment with erlotinib or the combination of nivolumab and erlotinib. The primary objective of Group D is to compare PFS of the combination of nivolumab and erlotinib versus erlotinib alone; comparisons of OS, ORR, and DOR are secondary objectives.
- Group E will evaluate the safety of combination therapy of nivolumab and crizotinib as first-line treatment in NSCLC, PS 0-2 ALK-positive subjects. The primary objective of Group E is to describe the safety and tolerability of nivolumab in combination with crizotinib; the secondary objectives are to describe PFS and ORR.

Subjects currently on treatment may continue to be treated and monitored as specified in the protocol. The decision to continue treatment should be based on the clinical judgment of the treating physician, in consultation with the patient.

As per Amendments 03 and 04, enrollment has closed for all groups.

Further details of the design of each Group A through E are provided in Section.2.1

2.1 Study Design

2.1.1 Treatment Group A: Maintenance, NSQ, PS 0-1, EGFRwt and ALKwt

Following first-line therapy with 4 to 6 cycles of Investigator's Choice of chemotherapy regimens (carboplatin or cisplatin plus paclitaxel plus bevacizumab or carboplatin or cisplatin plus pemetrexed), subjects showing no signs of progression, will be randomized (1:1:1) to receive maintenance therapy on 1 of 6 arms. Subjects under consideration for Group A are to complete the entire cycle 4 to 6-week of induction chemotherapy without disease progression prior to being

consented for this study. The maintenance treatment is to start within 42 days of completing induction chemotherapy.

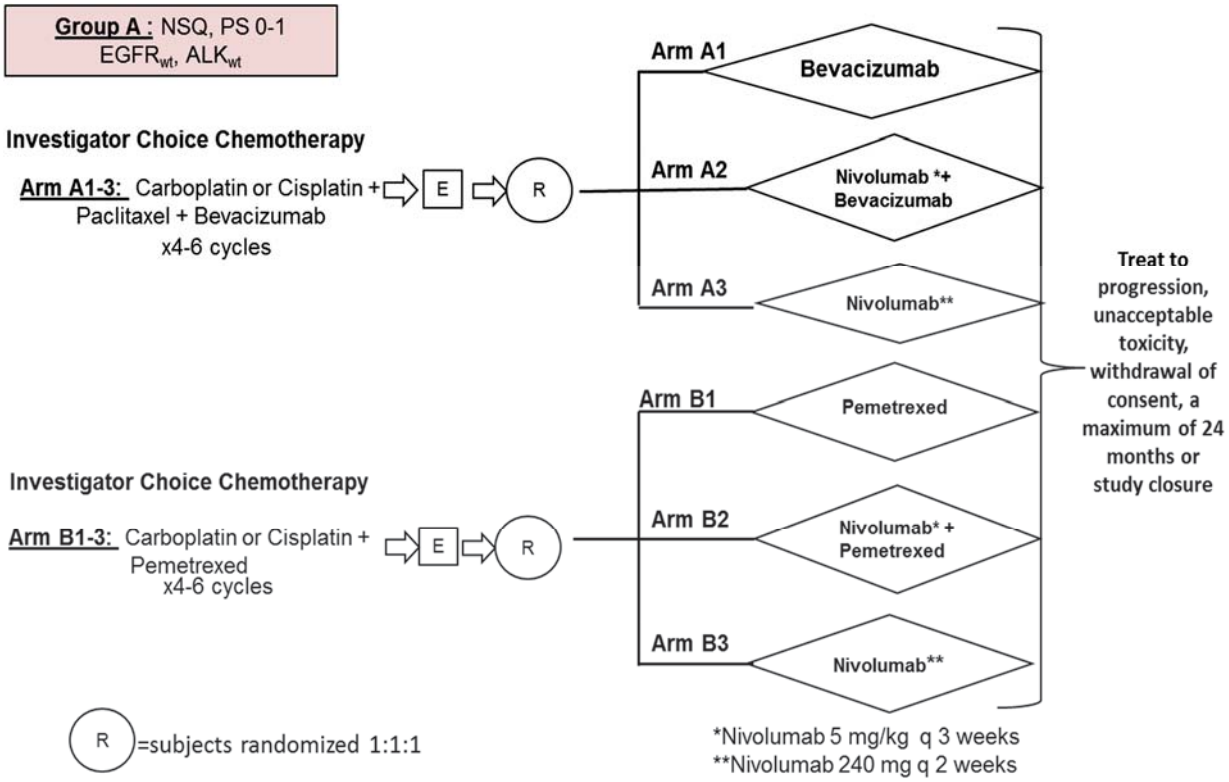
- Arm A1: bevacizumab 15 mg/kg every 3 weeks
- Arm A2: bevacizumab 15 mg/kg + nivolumab 5 mg/kg every 3 weeks over 30-minute infusion
- Arm A3: nivolumab 240 mg every 2 weeks over 30-minute infusion
- Arm B1: pemetrexed 500 mg/m2 every 3 weeks
- Arm B2: pemetrexed 500 mg/m2 every 3 weeks + nivolumab 5 mg/kg every 3 weeks over 30-minute infusion
- Arm B3: nivolumab 240 mg every 2 weeks

Pemetrexed premedication regimen: folic acid and vitamin B12, and dexamethasone are to be given per local institution standard and package insert.

Pemetrexed and bevacizumab administration is to follow their package insert. Subjects will be considered on-study once randomized to a maintenance therapy arm (beginning of Cycle 1). On-study tumor assessments will begin at Week 9 (± 1 week) and be performed every 8 weeks (± 1 week) for up to 2 years.

The schematic for Group A is presented in Figure 2.1.1-1.

Figure 2.1.1-1: Group A Schematic - Maintenance Therapy in subjects with NSQ NSCLC and PS 0-1, without EGFR and ALK Mutations



Note: The maintenance treatment is to start within 42 days of completing induction chemotherapy. Subjects who completed bevacizumab-containing induction chemotherapy will only be randomized to Arm A1, A2 or A3 and subjects who completed pemetrexed-containing induction chemotherapy will only be randomized to Arm B1, B2 or B3.
ALK=anaplastic lymphoma kinase; E=enrolled; EGFR=epidermal growth factor receptor; NSQ=non-squamous cell carcinoma; NSCLC = non-small cell lung cancer; PS=performance status; q=every; R=randomized; wt=wild type.

2.1.2 Treatment Group B: Maintenance, SQ, PS 0-1

Following initial therapy with 4 to 6 cycles of Investigator's Choice of chemotherapy regimens (carboplatin or cisplatin plus paclitaxel, carboplatin or cisplatin plus gemcitabine, carboplatin or cisplatin plus docetaxel, carboplatin or cisplatin plus albumin bound paclitaxel, carboplatin or cisplatin plus etoposide, carboplatin or cisplatin plus vinorelbine), subjects in Group B, showing no signs of progression, will be randomized (1:1) to maintenance therapy with either single-agent nivolumab (240 mg every 2 weeks) or BSC. Subjects under consideration for Group B are to complete the entire 4-6 week cycle of induction chemotherapy without disease progression prior to being consented for this study. Subjects will be considered on-study once randomized to a maintenance therapy arm (beginning of Cycle 1).On-study tumor assessments will begin at Week 9 (± 1 week) and be performed every 8 weeks (± 1 week) for up to 2 years.

The Group B schematic is presented in Figure 2.1.2-1.

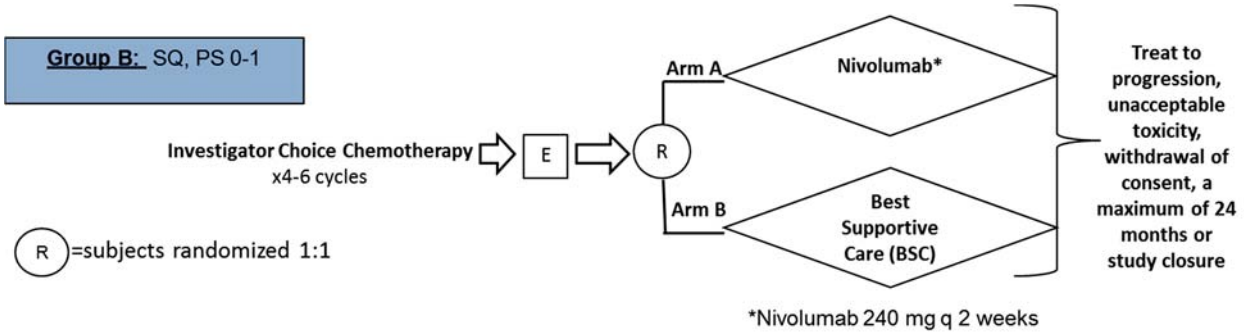
Best supportive care arm may include palliative radiation therapy or palliative surgery. The major components of BSC include:

- Adequate control of pain and other symptoms
- Identification of distressing symptom
- Support and assist decision making
- Illness understanding/education
- Coping with life-threatening illness
- Indicate referrals to other care providers

Symptom management includes but is not limited to:

- Pain
- Pulmonary symptoms (cough, dyspnea)
- Fatigue and sleep disturbance
- Mood (depression and anxiety)
- Gastrointestinal (anorexia and weight loss, nausea and vomiting, constipation).

Figure 2.1.2-1: Group B Schematic - Maintenance Therapy in Subjects with SQ NSCLC and PS 0-1



Note: The maintenance treatment is to start within 42 days of completing induction chemotherapy. BSC=best supportive care; E=enrolled; NSCLC=non-small cell lung cancer; R=randomized; PS=performance status; q=every; SQ=squamous cell carcinoma.

2.1.3 Treatment Group C: First-line, NSQ and SQ, PS 2, EGFRwt and ALKwt

Subjects assigned to Group C will be randomized (1:1) to receive first-line therapy with either: 4 to 6 cycles of Investigator's Choice of chemotherapy (Arm A) or single-agent nivolumab (Arm B).

The list of Investigator's Choice chemotherapy regimens is referenced from NCCN guideline 2015-20th annual edition.

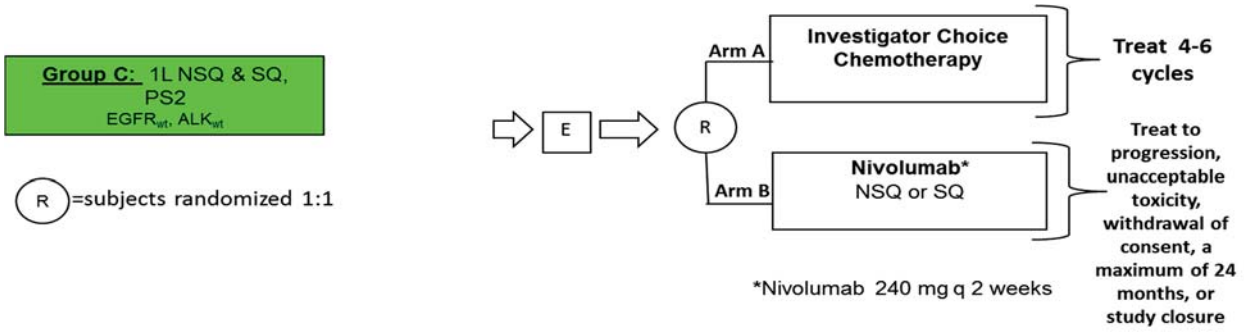
Investigator's Choice chemotherapy regimens will be as follows:

- Arm A (NSQ):
  - Carboplatin AUC = 6 + nab-paclitaxel 100mg/m^2 Days 1, 8, and 15 every 3 weeks
  - Carboplatin AUC = 6 + paclitaxel 200 mg/m^2 every 3 weeks
  - Carboplatin AUC = 6 + pemetrexed 500 mg/m^2 every 3 weeks
  - Carboplatin AUC = 6 + docetaxel 75 mg/m^2 every 3 weeks
  - Paclitaxel 175-225 mg/m^2 every 3 weeks
  - Docetaxel 60-75 mg/m^2 every 3 weeks
  - Gemcitabine 1000 mg/m^2 Days 1 and 8 every 3 weeks
  - Pemetrexed 500 mg/m^2 every 3 weeks
- Arm A (SQ):
  - Carboplatin AUC = 6 + nab-paclitaxel 100mg/m^2 Days 1, 8, and 15 every 3 weeks
  - Carboplatin AUC = 6 + paclitaxel 200 mg/m^2 every 3 weeks
  - Carboplatin AUC = 5 + gemcitabine 1000 mg/m^2 Days1 and 8 every 3weeks
  - Carboplatin AUC =6 + docetaxel 75 mg/m^2 every 3 weeks
  - Paclitaxel 175-225 mg/m^2 every 3 weeks
  - Docetaxel 60-75 mg/m^2 every 3 weeks
  - Gemcitabine 1000 mg/m^2 days 1 and 8 every 3 weeks
- Arm B (SQ or NSQ):
  - Nivolumab 240 mg every 2 weeks over 30 minute IV infusion

Subjects may receive optional maintenance therapy after initial chemotherapy in control group receiving Investigator's Choice chemotherapy per investigator decision of maintenance regimen according to NCCN guideline.

Subjects will be considered on-study once randomized to a treatment arm (beginning of Cycle 1). On-study tumor assessments will begin at Week 9 (± 1 week) and will be performed every 8 weeks (± 1 week) for up to 2 years. The study design schematic is presented in Figure 2.1.3-1.

Figure 2.1.3-1: Group C Schematic - First-line Treatment in NSQ or SQ NSCLC Subjects with PS 2, without EGFR and ALK Mutations



ALK=anaplastic lymphoma kinase; E=enrolled; EGFR=epidermal growth factor receptor; NSCLC=non-small cell lung cancer; NSQ=non-small cell carcinoma; R=randomized; PS=performance status; q=every; SQ=squamous cell carcinoma; wt=wild-type.

2.1.4 Treatment Group D: First-line, PS 0-2, EGFRmut

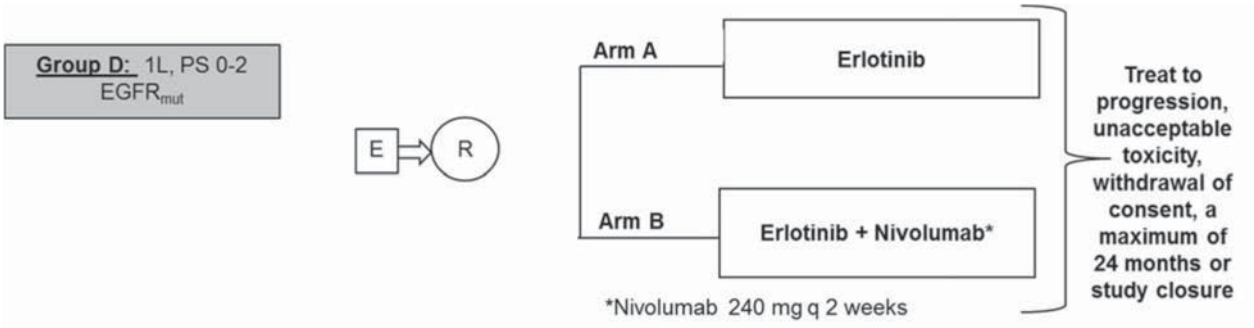
Subjects in Group D will be randomized (1:1) to treatment with erlotinib monotherapy or the combination therapy (erlotinib plus nivolumab) as follows:

- Arm A: erlotinib 150 mg QD
- Arm B: nivolumab 240 mg every 2 weeks + erlotinib 150 mg QD

Treatment for both arms will continue until disease progression, discontinuation due to unacceptable toxicity, withdrawal of consent, or up to a maximum of 24 months, whichever occurs first. Subjects must continue to meet all applicable inclusion and exclusion criteria.

On-study tumor assessments will begin at Week 9 (± 1 week) and be performed every 8 weeks (± 1 week) for up to 2 years. The study design schematic is presented in Figure 2.1.4-1.

Figure 2.1.4-1: Group D Schematic - First-line Treatment in Subjects with PS 0-2, and EGFR mutations



E=enrolled; EGFR=epidermal growth factor receptor; mut=mutation; R=randomized; PS=performance status; q=every.

2.1.5 Treatment Group E: First-line, PS 0-2, ALK-positive

Subjects in Group E will receive the combination therapy of nivolumab (240 mg every 2 weeks) and crizotinib (250 mg BID). On-study tumor assessments will begin at Week 9 and will be performed every 8 weeks (± 1 week) for up to 2 years.

The study design schematic is presented in Figure 2.1.5-1.

When the 20th patient is enrolled and reaches Week 17, DMC safety review of this cohort will be triggered. "Safe" is defined as ≤ 20% of treated subjects with drug-related AEs leading to discontinuation of both drugs by Week 17.

Figure 2.1.5-1: Group E Study Schematic - First-Line Treatment in Subjects with PS 0-2, and ALK-positive

ALK=anaplastic lymphoma kinase; E=enrolled; q=every; PS=performance status.

Per Amendment 03, this group is closed and all the ongoing subjects have been discontinued from the combination treatment of crizotinib and nivolumab

Close liver function monitoring has been recommended:

- All subjects are to undergo twice weekly liver function testing through 60 days following the last dose of nivolumab.
- Subjects with normal results for liver function are to undergo once weekly liver function testing from 61 days through 100 days following the last dose of nivolumab.
- Subjects with an abnormal result for liver function within 100 days of the last dose of nivolumab, are to undergo twice weekly liver function testing.

Additional liver function monitoring should be based on the clinical judgment of the treating physician.

2.2 Treatment Assignment

Subjects will be enrolled using an Interactive Response System (IVRS). During the enrollment period, a subject will provide signed informed consent and their study eligibility will be established. Subjects meeting enrollment criteria for Groups A, B, C, or D will be randomized to treatment arms as described in Sections 2.1.1, 2.1.2, 2.1.3, or 2.1.4 using IVRS. Subjects in Group E are not randomized.

For Groups A and B, randomization will be stratified by:

1) Disease status (recurrent locally advanced vs. metastatic)
2) Response (complete response/partial response/stable disease) to induction chemotherapy
3) History of ablative/definitive radiation therapy to oligometastasis post induction therapy (yes vs. no).

For Group C, randomization will be stratified by:

1) Disease status (recurrent locally advanced vs. metastatic)
2) Tumor histology (NSQ vs. SQ).

For Group D, randomization will be stratified by:

1) Disease status (recurrent locally advanced vs. metastatic)
2) Performance status (ECOG 0, 1 or 2).

2.3 Blinding and Unblinding

This is an open-label study. Blinding is not applicable. However, to reduce bias, the study team from the Sponsor and the CRO/vendors who are involved in the trial conduct will be blinded for the aggregated data at the treatment level until the trial database lock.

The Data Monitoring Committee (DMC) will be provided with unblinded data in order to ensure the ongoing safety and efficacy of the trial. Data unblinding as required for the DMC review will be conducted on an ongoing basis by a data manager/statistician or CRO not involved in the trial conduct in order to keep the trial team blinded.

2.4 Protocol Amendments

Revised Protocol 01 (31-Jul-2015) incorporates Amendment 01:

1) Sample size
   a) Group A corrected to 765
2) To simplify the study design for Group D
   a) Removed central testing for EGFR mutation
   b) Removed independent imaging review

3) To modify biomarker sample collection
   a) The timing on whole blood, serum and tissue collection is simplified to be consistent with project standard.
   b) Plasma sample for circulating tumor DNA is added to Group D
   c) Addition of HCRU assessments to Groups A, C and D

Revised Protocol 02 (29-Oct-2015) incorporates Administrative Letter 01:

1) Addresses inconsistencies in the previous version

Revised Protocol 03 (28-Sep-2016) incorporates Amendment 02:

To updates the Adverse Event Management Algorithms for

1) Nivolumab per Investigator Brochure Version 15 & Erratum 01 to Investigator Brochure
2) Version 15
3) To update the Study Director/Medical Monitor
4) To address inconsistencies/errors
5) To add cisplatin as one of platinum-based chemotherapies for consistence and for flexibility for the induction therapy
6) The adverse event collection for Group B, Arm B (Best Supportive Care) was updated to commerce at randomization for clarification and consistence
7) To clarify information from the previous version

Revised Protocol 04 (28-Mar-2017) incorporates Amendment 03

1) Amendment to close enrollment for Groups A, B, C, and E.
2) To note that Group E will receive no further treatment, and to add additional monitoring for liver toxicity through follow up in these subjects.
3) Pregnancy language was updated.

Revised Protocol 05 (26-Mar-2018) incorporates Amendment 04

1) Amendment to closes enrollment for Group D
2) Clarified statistical treatment of subjects who received any subsequent anti-cancer therapy without previously reported progression
3) Updated the actual samples sizes for study groups after closing enrollment and statistical analyses
4) Added rationale for closing enrollment for Group D
5) Updated timing of tumor assessments during study
6) Changed the collection of survival status from 5 years to 4 years

[redacted]

9) Updated protocol with current program safety language for dose modifications and discontinuations
10) Updated protocol with current program contraception language

2.5 Data Monitoring Committee and Other External Committees

A DMC will be established to provide oversight of safety and efficacy considerations in protocol CA209370, and to provide advice to the sponsor regarding actions the committee deems necessary for the continuing protection of subjects enrolled in the trial. The DMC will be charged with assessing such actions in light of an acceptable benefit/risk profile for nivolumab. The DMC will act in an advisory capacity to BMS and will monitor subject safety and evaluate the efficacy data for the study. Efficacy will also be reviewed by the DMC - as part of the benefit-to-risk assessment and for the formal analyses of PFS and OS.

The DMC will be advisory to the clinical study leadership team. The clinical study leadership team will have responsibility for overall conduct of the study including managing the communication of study data. The group will be responsible for promptly reviewing the DMC recommendations, for providing guidance regarding the continuation or termination of the study, and for determining whether to continue enrollment or follow-up.The oncology therapeutic area of BMS has primary responsibility for design and conduct of the study. Details of DMC responsibilities and procedures are specified in the DMC charter [25].

3 OBJECTIVES

The primary, secondary, and exploratory objectives are summarized in Table 3-1.

Table 3-1: Study Objectives

	Primary Objectives	Secondary Objectives	[redacted]
Group A: Maintenance, NSQ, PS 0-1, $EGFR_{wt}$ and ALK_{wt}	To compare PFS[a] and OS of maintenance treatment with bevacizumab versus nivolumab or bevacizumab versus nivolumab + bevacizumab (Arm A) or pemetrexed versus nivolumab or pemetrexed versus nivolumab + pemetrexed (Arm B)	• To compare duration of response (DOR) and objective response rate (ORR) of maintenance treatment with bevacizumab versus nivolumab or bevacizumab versus nivolumab + bevacizumab (Arms A1, A2, A3) or pemetrexed versus nivolumab or pemetrexed versus nivolumab + pemetrexed (Arms B1, B2, B3)	

Table 3-1: Study Objectives

	Primary Objectives	Secondary Objectives	[redacted]
Group B: Maintenance, SQ, PS 0-1	To compare PFS[a] and OS of maintenance treatment with single-agent nivolumab versus BSC	• To compare DOR and ORR of maintenance treatment with single-agent nivolumab versus BSC	
Group C: First-line, NSQ and SQ, PS 2, $EGFR_{wt}$ and ALK_{wt}	The primary objective will be to compare PFS and OS of single-agent nivolumab versus investigator's choice chemotherapy	• To compare DOR and ORR of nivolumab versus investigator's choice chemotherapy	
Group D: First-line, PS 0-2, $EGFR_{mut}$	To compare PFS with the combination of nivolumab plus erlotinib versus erlotinib	• To compare OS, ORR, and DOR of the combination of nivolumab plus erlotinib versus erlotinib alone	

Table 3-1: Study Objectives

	Primary Objectives	Secondary Objectives	[redacted]
Group E: First-line, PS 0-2, ALK-positive	To estimate the incidence of treatment-related (nivolumab + crizotinib) AEs leading to study drug discontinuation	• To describe PFS of combination therapy • To assess ORR associated with combined Nivolumab and crizotinib therapy	

a Progression-free survival (PFS) is defined as the time from randomization to the date of the first documented tumor progression, as determined by investigators (per RECIST v1.1), or death due to any cause, whichever occurs first.

AE=adverse events; ALK=anaplastic lymphoma kinase, BSC=best supportive care; CR=complete response; DCR=disease control rate; DOR=duration of response; ECOG=Eastern Cooperative Oncology Group; EGFR=epidermal growth factor receptor; mut=mutation; NSCLC=non-small cell lung cancer; NSQ=non-squamous; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PR=partial response; PS=performance status; SD=stable disease; SQ=squamous; WT=wild-type.

4 ENDPOINTS

- Disease control rate (DCR) is defined as the number of subjects that achieved a best overall response of CR, PR, or SD, divided by the total number of randomized subjects with measurable disease at baseline. (This endpoint is for Group D only.)
- Duration of response (DOR) is defined as the time from first confirmed response (CR or PR) to the date of the initial objectively documented tumor progression as determined using RECIST 1.1 criteria or death due to any cause, whichever occurs first. For subjects who neither progress nor die, the DOR will be censored on the date of their last evaluable tumor assessment. DOR will only be evaluated in subjects with objective response of CR or PR
- Objective response rate (ORR) is defined as the number and percentage of subjects with a best overall response (BOR) of confirmed complete response (CR) or partial response (PR). Best overall response (BOR) is defined as the best response designation, recorded between the date of first dose and the date of the initial objectively documented tumor progression per RECIST v1.1 or the date of subsequent therapy, whichever occurs first. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR determination.
- Overall survival (OS) is defined as the time from randomization to the date of death. A subject who has not died will be censored at last known date alive. OS will be followed continuously

while subjects are on the treatment and every 3 months via in-person or phone contact after subjects discontinue the study drug.

- Progression-free survival (PFS) is defined as the time from randomization to the date of the first documented tumor progression, as determined by investigators (per RECIST v1.1), 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 assessment and did not die will be censored on the first dosing date.
- Subjects who received any subsequent anti-cancer therapy (including on-treatment palliative radiation therapy of non-target bone lesions or CNS lesions) without a prior reported progression will be censored at the last evaluable tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy.
- Group E PFS and OS are defined as the time from first treatment to the date of event since there is no randomization in this group.
- Group C Patient Reported Outcome (PRO) data from the EQ-5D and FACT-L, will be assessed by measuring change from baseline at each assessment point and disease-related symptom improvement rate as reported by the FACT-L.
- All safety data will be summarized and listed for all treated subjects. All on-study AEs, SAEs, treatment-related AEs, and treatment-related SAEs, etc. will be summarized using worst grade per NCI CTCAE v4.0 by system organ class and preferred term. On-study lab abnormalities including hematology, chemistry, liver function, thyroid function, and renal function will be summarized using worst grade per NCI CTCAE v4.0 criteria.

4.1 Primary Endpoints

Group A: PFS and OS

Group B: PFS and OS

Group C: PFS and OS

Group D: PFS

Group E: Incidence of treatment-related AEs leading to both study drugs discontinuation.

4.2 Secondary Endpoints

Group A: DOR and ORR

Group B: DOR and ORR

Group C: DOR and ORR

Group D: OS, DOR, and ORR

Group E: PFS, and ORR

[redacted]

[redacted]

5 SAMPLE SIZE AND POWER

5.1 Group A through D sample size determination

A decision was made in December 2016 to stop enrollment for Groups A, B, and C, and stop enrollment and treatment for Group E. Sample sizes for these groups will be the number of patients already randomized (treated in Group E).

A decision was made in December 2017 to stop enrollment for Group D. As a result of this decision, the actual sample sizes for these groups are indicated in the following table. Therefore, the overall population randomized or enrolled in this Master Protocol is now approximately 342 subjects.

Group	Sample Size
A	132
B	35
C	52
D	109
E	14

The following is the rationale of the original sample size determination.

This is a Phase 1/2, open-label, Master Protocol with 5 groups/sub-studies. The planned overall population to be enrolled in this Master Protocol was approximately 1953 subjects at maximum. Individual sample sizes per group are shown in Table 5.1-1. The sample size for each Group depends on the population, treatment effect, and primary endpoint for each group.

Table 5.1-1: Maximum Sample Size and Comparisons of Interest

Population	Maximum Sample Size	Primary Endpoint	Comparisons of Interest
Group A: Maintenance, NSQ, PS 0-1, EGFRwt and ALKwt	765 1:1:1 randomization in bevacizumab containing arms. 1:1:1 randomization in pemetrexed containing arms	PFS/OS	1. Nivolumab vs. bevacizumab for PFS 2. Nivolumab vs. bevacizumab for OS 3. Nivolumab plus bevacizumab vs. bevacizumab for PFS 4. Nivolumab plus bevacizumab vs. bevacizumab for OS 5. Nivolumab vs. pemetrexed for PFS 6. Nivolumab vs. pemetrexed for OS 7. Nivolumab plus pemetrexed vs. pemetrexed for PFS 8. Nivolumab plus pemetrexed vs. pemetrexed for OS
Group B: Maintenance, SQ, PS 0-1	500 1:1 randomization	PFS/OS	Nivolumab vs. Best supportive care
Group C: First-line, NSQ and SQ, PS 2, $EGFR_{wt}$ and ALK_{wt}	350 1:1 randomization	PFS/OS	Nivolumab vs. Investigator choice chemotherapy for superiority and non-inferiority
Group D: First-line, PS 0-2, EGFRmut	318 1:1 randomization	PFS	Nivolumab plus Erlotinib vs. Erlotinib
Group E: First-line, PS 0-2, ALK-positive	20 Single arm, No randomization	Incidence of drug-related AEs leading to discontinuation	Not Applicable

AE=adverse event; PFS=progression-free survival; OS=overall survival.

The adaptive trial is designed to identify an appropriate sample size and follow-up duration based upon accruing information to produce sufficient power in each group for a range of potential effect sizes and PFS/OS rates rather than provide a fixed power for one particular expected effect size and PFS/OS rate which may prove to be incorrect once we observe trial data.

The values below illustrate high power for one possible value of expected benefit in the nivolumab vs. control arms. Full operating characteristics over a broader range of possible median PFS values, OS values, and hazard ratios are shown in the full adaptive design plan, available upon request.

For example, Group A, assuming median control (Pem or Bev) PFS of 5 months and a median of 7.5 months in the nivolumab and nivolumab combination arms to produce a hazard ratio of 0.67, the design offers 91% power in the Nivo vs. Pem comparisons and 64/74% in the Nivo alone/Nivo-combination vs. Bev comparisons, respectively. This also assumes that 80% of patients will have previously taken pemetrexed vs. 20% on bevacizumab.

Group A, assuming median control (Pem or Bev) OS of 21 months and a median of 29 months in the nivolumab and nivolumab combination arms to produce a hazard ratio of 0.72, the design offers 86% power in the Nivo vs. Pem comparisons and 57% in the Nivo vs. Bev comparisons. This also assumes that 80% of patients will have previously taken pemetrexed vs. 20% on bevacizumab.

Group B, assuming true but unknown hazard ratios of 0.75 for both PFS (5.5 vs. 7.3 months) and OS (13.1 vs. 17.4 months), 500 patients provides 86% power for PFS and 99% power for OS. If the OS hazard ratio decreases to 0.79 (13.1 vs. 16.6 months), then 500 patients still offers 93% power for OS.

Group C, assuming true but unknown hazard ratios of 0.73 for both PFS (3.5 vs. 4.8 months) and OS (7.2 vs. 9.9 months), 350 patients provides 80% power for PFS and 96% power for OS. If the OS hazard ratio decreases to 0.79 (7.2 vs. 9.3 months), then 350 patients still offers 84% power for OS.

Group D, assuming true but unknown hazard ratios of 0.63 for PFS (10 vs. 16 months), the design provides 91% power for PFS.

Full operating characteristics over a broader range of possible median PFS values, OS values, and hazard ratios are shown in the full adaptive design plan, and available upon request.

5.2 Group E sample size determination

[redacted]

In order to characterize the safety and tolerability, this study will treat with novel combination: nivolumab and crizotinib in 20 subjects who have recurrent locally advanced or metastatic NSCLC. This sample size will allow estimating an approximate incidence rate of 5% (n=1 subjects with nivolumab treatment-related adverse events) with a 95% CI (confidence interval) of (0.13%, 24.9%), or an incidence rate of 40% (n=8 subjects with events) with a 95% CI of (19.12%, 63.95%).

Estimated 95% CIs for various event rates for a population of 20 subjects are described in Table 5.2-1. The goal is to identify safe regimen for future development and “safe” is defined as ≤ 20% treated subjects with drug-related AEs leading to drug discontinuation by Week 17.

Table 5.2-1: Estimated Incidence

Estimated Incidence Rates and 95% CIs			
Sample Size	Incidence Rate (%)	Lower 95% CI (%)	Upper 95% CI (%)
20	5.0	0.13	24.90
20	10.0	1.23	31.70
20	15.0	3.21	37.89
20	20.0	5.73	43.66
20	25.0	8.66	49.10
20	30.0	11.89	54.28
20	35.0	15.39	59.22
20	40.0	19.12	63.95
20	45.0	23.06	68.47
20	50.0	27.20	72.80

CI=confidence interval.

Due to observed hepatic toxicity, Group E was permanently terminated with 13 subjects treated with the combination treatment of nivolumab and crizotinib.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

- Unless otherwise specified, the below definitions are applied to all groups/sub-studies. Baseline period:
  - Baseline evaluations or events will be defined as evaluations or events that occur before the date and time of the first dose/randomization of study treatment for safety analyses/efficacy analyses.
  - 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, vital signs and other safety assessments) 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 on the same date (and time, if collected), the assessment with the latest database entry date (and time, if collected) will be considered as baseline.

- 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 included if event occurred within a safety window of 30 days (or 100 days depending on the analysis) after the last dose of study treatment.

– On-treatment evaluations (laboratory tests and vital signs) will be defined as evaluations taken after the day (and time, if collected and not missing) of first dose of study treatment. For subjects who are off study treatment, evaluations should be within a safety window of 30 days (or 100 days depending on the analysis) after the last dose of study treatment.

6.2 Treatment Regimens

- For randomized sub-studies (Groups A-D)**, treatment group "as randomized"** corresponds to the treatment group assigned by the IVRS system
- The treatment group "as treated" will be same as the treatment group "as randomized" by IVRS unless a subject received the incorrect study treatment for the entire period of treatment, in which case the subject's treatment group "as treated" will be defined as the incorrect study treatment.

Unless otherwise specified, the safety analysis will be based on the treatment group "as treated".

Group A: This group will enroll 2 cohorts, subjects who have completed 4-6 cycles of 1) bevacizumab, carboplatin, and paclitaxel or 2) pemetrexed and carboplatin. In the first cohort, subjects will be randomized 1:1:1 to

1) Arm A1: bevacizumab (15 mg/kg IV q3 weeks)
2) Arm A2: bevacizumab (15 mg/kg IV q3 weeks) + nivolumab (5 mg/kg IV q3 weeks)
3) Arm A3: nivolumab (240 mg IV q2 weeks)

In the second cohort, subjects will be randomized 1:1:1 to

1) Arm B1: pemetrexed (500 mg/m^2 IV q3 weeks)
2) Arm B2: pemetrexed (500 mg/m^2 IV q3 weeks) + nivolumab (5 mg/kg IV q3 weeks)
3) Arm B3: nivolumab (240 mg IV q2 weeks)

Treatment Arms Comparisons for Group A:

Arm A3 vs. Arm A1

Arm A2 vs. Arm A1

Arm B3 vs. Arm B1

Arm B2 vs. Arm B1

Group B: The subjects in this group will be randomized 1:1 to

1) Arm A: nivolumab (240 mg IV q2 weeks)
2) Arm B: Best Supportive Care

Treatment Arms Comparisons for Group B:

Arm A vs. Arm B

Group C: The subjects in this group will be randomized 1:1 to

1) Arm A (NSQ): Investigator's Choice of Chemotherapy:

- Carboplatin AUC = 6 + nab-paclitaxel (100 mg/m^2) Days 1, 8, and 15 q3 weeks
- Carboplatin AUC = 6 + paclitaxel (200 mg/m^2) q3 weeks
- Carboplatin AUC = 6 + pemetrexed (500 mg/m^2) q3 weeks
- Carboplatin AUC = 6 + docetaxel (75 mg/m^2) every 3 weeks
- Paclitaxel (175-225 mg/m^2) q3 weeks
- Docetaxel (60-75 mg/m^2) q3 weeks
- Gemcitabine (1000 mg/m^2) Days 1 and 8 q3 weeks
- Pemetrexed (500 mg/m^2) q3 weeks

Arm A (SQ): Investigator's Choice of Chemotherapy:

- Carboplatin AUC = 6 + nab-paclitaxel (100 mg/m^2) Days 1, 8, and 15 q3 weeks
- Carboplatin AUC = 6 + paclitaxel (200 mg/m^2) q3 weeks
- Carboplatin AUC = 5 + gemcitabine (1000 mg/m^2) Days1 and 8 q3 weeks
- Carboplatin AUC =6 + docetaxel (75 mg/m^2) q3 weeks
- Paclitaxel (175-225 mg/m^2) q3 weeks
- Docetaxel (60-75 mg/m^2) q3 weeks
- Gemcitabine (1000 mg/m^2) days 1 and 8 q3 weeks

2) Arm B (NSQ or SQ): nivolumab (240 mg IV q2 weeks)

Treatment Arms Comparisons for Group C:

Arm B vs. Arm A

Group D: Subjects in Group D will be randomized (1:1) to treatment with erlotinib monotherapy or the combination therapy (erlotinib plus nivolumab) as follows:

1) Arm A: erlotinib (150 mg QD)
2) Arm B: nivolumab (240 mg IV q2 weeks) + erlotinib (150 mg QD)

Treatment Arms Comparisons for Group D:

Arm B vs. Arm A

Group E: randomization is not applicable, single arm study: nivolumab (240 mg IV q2 weeks) + crizotinib (250 mg BID)

6.3 Populations for Analyses

Group A: Subjects with histologically confirmed Stage 4 or recurrent locally advanced NSQ NSCLC. Subjects enrolled must have completed 4-6 cycles of bevacizumab, carboplatin, and paclitaxel and without disease progression; or have completed 4-6 cycles of pemetrexed and carboplatin without disease progression. ECOG 0 – 1.

Group B: Subjects with histologically confirmed Stage 4 or recurrent locally advanced SQ NSCLC. Enrolled subjects must have completed 4-6 cycles of SOC chemotherapy, and without disease progression. ECOG performance status 0-1.

Group C: First-line treatment of subjects with histologically confirmed Stage 4 or recurrent locally advanced NSCLC and with ECOG Performance Status of 2 with wild-type EGFR and ALK alleles.

Group D: First-line treatment for subjects with histologically confirmed Stage 4 or recurrent locally advanced EGFR-mutated NSCLC, with ECOG performance status of 0 – 2.

Group E: First-line treatment for subjects with histologically confirmed Stage 4 or recurrent locally advanced ALK-positive NSCLC, with ECOG performance status of 0 – 2.

- **All randomized subjects**: All subjects who were randomized (applies to Groups A-D) to any treatment arm in the study. This is the primary dataset for analyses of demography, protocol deviations, baseline characteristics, efficacy, outcome research and biomarker PD-L1 expression.
- **All enrolled subjects**: All subjects who signed an informed consent form. Analyses of the patients enrolled into the study but not randomized and the reason for not being randomized will be performed on the data set of all enrolled subjects. All enrolled subjects set will be used as primary dataset for the Group E analyses of study population.
- **All treated subjects**: All subjects who received at least one dose of any study drug. This is the primary dataset for analyses of exposure and safety analysis (applies to Groups A-E). This is the primary dataset for analyses of study conduct, demography, baseline characteristics, efficacy, outcome research and biomarker for Group E.
- **All response evaluable subjects**: All randomized subjects who have baseline and at least one on-study evaluable tumor measurement
- **All PD-L1 tested subjects**: All subjects, randomized or not, who had a tumor biopsy specimen available for PD-L1 expression testing (validated assay). This includes both randomized and screen failure subjects.
- **All randomized subjects with quantifiable PD-L1 expression at baseline:** see definition of baseline and quantifiable PD-L1 expression in Section 4.3.6.
- **Randomized subject with measurable disease at baseline –** A randomized subject is considered to have measurable disease at baseline if they have one or more baseline target lesion assessments where at least one target lesion measurement is at least (>=) 10 mm for a non-Lymph node tumor location or at least (>=) 15 mm for a Lymph node tumor location.

In general, efficacy will be analyzed for all randomized patients (except Group E for treated patients and for Groups A and B BOR will be evaluated for subjects with measurable disease at baseline) and safety will be analyzed for all treated patients.

7 STATISTICAL ANALYSES

7.1 General Methods

Unless otherwise specified:

- All analyses described below, summaries and listings are applicable for each Group A-E
- All analyses will be performed for each Group separately;
- Group A will be further separated for each Cohort in analyses;
- Summaries will be produced by treatment arms and total for all groups except Group E.

Unless otherwise noted, discrete variables will be tabulated by the frequency and proportion of subjects falling into each category, grouped by treatment (with total). Percentages given in these tables will be rounded to one decimal and, therefore, may not always sum to 100%. Percentages less than 0.1 will be indicated as '< 0.1'. Continuous variables will be summarized by treatment arm (with total) using mean, standard deviation, median, minimum, and maximum values.

Since Group E is a single arm study, analyses by treatment arm will consist only of one arm.

The conventions to be used for imputing partial dates for analyses requiring dates are described in Section 8.

7.1.1 Randomization Stratification Factors

Groups A-B: Disease Status (Recurrent Locally Advanced vs. Metastatic), Response to Prior Chemo (Complete Response vs. Partial Response vs. Stable Disease), History of ablative /definitive Radiation Therapy to oligometastasis post induction therapy (yes vs. no).

Group C: Disease Status (Recurrent Locally Advanced vs. Metastatic), Tumor Histology (NSQ vs. SQ)

Group D: Disease Status (Recurrent Locally Advanced vs. Metastatic), Performance Status (ECOG 0 vs.1 vs. 2).

Summaries of stratification factors by treatment arms will be provided for Group A, B and D.

7.1.2 Unblinding

Summaries and listings in this statistical analysis plan will be created using dummy treatment codes in order to reduce the study bias (section 2.3). The unblinding will be done by a separate biostatistics team not involved in the analysis of the study. The unblinded team will produce the summaries and listings using the developed SAS programs on true treatment codes and will provide the unblinded outputs to the DMC.

7.2 Study Conduct

7.2.1 Accrual

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

7.2.2 Relevant Protocol Deviations

The relevant protocol deviations will be summarized for all randomized (treated for Group E) subjects, by treatment arm and overall. Non-programmable significant eligibility and on-treatment protocol deviations will be reported through Clinical Trial Management System listings.

A subject listing will also be produced.

The following programmable deviations from protocol will be considered as relevant protocol deviations.

At Entrance:

- Eligibility criteria not met.

Criterion	Group A	Group B	Group C	Group D	Group E
i. Histology	a) Histologically confirmed recurrent locally advanced or Stage 4 NSQ NSCLC[a]	b) Histologically confirmed recurrent locally advanced or Stage 4 SQ NSCLC[a]	c) Histologically confirmed recurrent locally advanced or Stage 4 SQ or NSQ NSCLC[a]	d) Histologically confirmed recurrent locally advanced or Stage 4 NSCLC[a]	e) Histologically confirmed recurrent locally advanced or Stage 4 NSCLC[a]
ii. ECOG PS	a) 0-1		b) 2	c) 0-2	
iii. Prior induction therapy	a) 4-6 cycles of bevacizumab or pemetrexed containing induction chemo therapy with no evidence of disease progression	b) 4-6 cycles of induction chemo therapy with no evidence of disease progression	c) None	d) None	
iv. EGFR mutation[b]	a) Negative/wild type, or indeterminate	b) Primary SQ histology tumors are not required to be tested for EGFR mutation	c) Negative/wild type, or indeterminate. Primary SQ histology tumors are not required to be tested for EGFR mutation	d) Positive sensitizing mutation (exon 19 deletion, exon 21-L858R-substition)	e) Negative/wild type, or indeterminate

Criterion	Group A	Group B	Group C	Group D	Group E
v. ALK translocation[c]	a) Negative/wild type, or indeterminate				b)Positive
vi. RECIST 1.1	a) Measureable disease by CT within 21 days of study drug. Target lesions may be located in a previously irradiated field with radiographic evidence of disease progression in that site post-radiation therapy				
	b) Groups A and B: Subjects with CR/PR/SD to initial induction therapy are allowed to enroll		c) Not Applicable		
vii. Tissue requirement	a) Either a formalin-fixed, paraffin-embedded (FFPE) tissue block or minimum of 10 unstained tumor tissue sections, with an associated pathology report, must be submitted for biomarker evaluation prior to randomization. Biopsies of bone lesions that do not have a soft tissue component or decalcified bone tumor samples or cytology samples are also not acceptable.				

[a] According to the 7th International Association for the Study of Lung Cancer classification

[b] EGFR testing is not required if ALK or KRAS test is positive; ALK testing is not required if EGFR or KRAS test is positive; use of an FDA-approved test is strongly encouraged; appropriate documentation of the results must be available prior to randomization/treatment

[c] FDA-approved test is strongly encouraged for ALK translocation testing. Appropriate documentation of the test results must be available prior to randomization/ start of treatment

ALK=anaplastic lymphoma kinase, CR=complete response; ECOG=Eastern Cooperative Oncology Group; EGFR=epidermal growth factor receptor; FFPE=formalin-fixed paraffin-embedded; mut=mutation; NA=not applicable; NSCLC=non-small cell lung cancer; NSQ=non-squamous; PS=performance status; SQ=squamous; WT=wild-type.

Treatment Legend: Group A: Maintenance, NSQ PS 0-1, EGFRwt and ALKwt; Group B: Maintenance, SQ, PS 0-1; Group C: First-line NSQ and SQ, PS 2, EGFRwt and ALKwt; Group D: First-line PS 0-2, EGFRmut; Group E: First-line PS 0-2, ALK-positive

– Baseline laboratory criteria not met.

Test	Value
i. WBC	≥ 2000/uL
ii. Neutrophils	≥ 1500/uL
iii. Platelets	≥ 100x10^3/uL
iv. Hemoglobin	≥ 9.0 g/dL
v. Serum creatinine	≤1.5 ×ULN or calculated creatinine clearance > 40 mL/min using the Cockcroft-Gault formula: Female CrCl = (140- age in years) x weight in kg x 0.85/72 x serum creatinine in mg/ dL Male CrCl = (140- age in years) x weight in kg x 1.00/72 x serum creatinine in mg/ dL
vi. AST	≤ 3.0 ×ULN
vii. ALT	≤ 3.0 ×ULN
viii. Total Bilirubin	≤ 1.5 ×ULN (except subjects with Gilbert Syndrome who must have a total bilirubin level of < 3.0 ×ULN)

On-study:

- Subjects receiving prohibitive medications during treatment:
  - Immunosuppressive agents
  - Immunosuppressive doses of systemic corticosteroids (except as stated in protocol Section 3.4.3 permitted therapy)
  - Concurrent anti-cancer therapy (chemotherapy, hormonal therapy, immunotherapy, radiation therapy, standard or investigational agents for treatment of NSCLC).
- Subjects treated differently as randomized (subjects who received the wrong treatment, excluding the never treated).

7.3 Study Population

Summaries of study population will be based on all enrolled subjects and will present the number of subjects enrolled, randomized, not randomized, treated, not treated, all response evaluable and response not evaluable by treatment arms.

7.3.1 Disposition of Subjects

The total number of subjects randomized, randomized treated and randomized but not treated will be presented along with the reason for not being treated by treatment arm as randomized. This analysis will be performed on the all randomized population for Group A-D.

The total number of subjects enrolled, enrolled treated and enrolled but not treated will be presented along with the reason for not being treated. This analysis will be performed on the all enrolled population for Group E.

End of treatment period with the number of subjects who discontinued study treatment along with corresponding reason will be tabulated by treatment arm as treated.

A subject listing for all treated subjects will be provided showing the subject's randomization date, first and last dosing date and reason for going off-treatment, based on the treatment phase of the study. A subject listing for subjects not randomized or treated will also be provided, showing the subject's race, gender, age, consent date and reason for not being randomized or treated.

7.3.2 Demographic and Other Baseline Characteristics

Demographic, baseline disease characteristics and baseline laboratory results will be summarized using descriptive statistics for all treated subjects and all randomized subjects in each Group.

Demographic characteristics:

- Age
- Age category I (<65,65-<75, ≥75)
- Age category II (<70, ≥70)
- Gender
- Race/Ethnicity

Initial Disease Characteristics:

- Disease Stage at Diagnosis (Stage 0/IA/IB/IIA/IIB/IIIA/IIIB/IVA/IVB)
- Cell Type (Adenocarcinoma, Squamous Cell Carcinoma, Large Cell Carcinoma, Broncho-alveolar Carcinoma, Other)
- Time from initial diagnosis to randomization/start of treatment (mean, SD; categories will be defined based on the data)

Current Disease Characteristics:

- Disease Stage at Study Entry (Stage IIIA/IIIB/IVA/IVB)
- Cell Type (Adenocarcinoma, Squamous Cell Carcinoma, Large Cell Carcinoma, Broncho-alveolar Carcinoma, Other)

Other Baseline Characteristics:

- Baseline tumor histology
- Previously irradiated tumor lesions appeared/progressed since the completion of radiotherapy (Yes/No)
- Tobacco Use (current, former, never, unknown)
- Baseline Height
- Baseline Weight
- Body surface area (BSA)
- Performance Status ECOG (0,1,2)
- Target Lesions: Assessment of target lesions (Yes/No), if Yes: Tumor code (list from the database), site of target lesion, procedures for evaluating target lesion (list from the database), target lesion measurement in mm, target lesion evaluation for non-measurable lesions (too small to measure, lesion split, lesion merged, unable to determine, procedure not done, lesion not evaluated)
- Non-target lesions: Assessment of target lesions (Yes/No), if Yes: Tumor code (list from the database), site of target lesion, procedures for evaluating target lesion (list from the database).
- Baseline EGFR Mutation Status: Assay results available (Yes/No), if Yes: Mutations (list from the database), Method (list from the database) (for Group D)
- Baseline ALK Mutation Status: Assay results available (Yes/No), if Yes: Mutations (list from the database), Method (list from the database) (for Group E)
- Baseline K-RAS mutation status
- Baseline MET receptor status
- Baseline any other mutation status reported

7.3.3 Medical History

General medical history will be listed by subject and pretreatment events will be tabulated.

7.3.4 Baseline Examinations

Subjects with abnormal baseline physical exam results will be tabulated by examination criteria (e.g., neck, cardiovascular, lungs, etc.) and by treatment arm as randomized. A by subject listing will be provided.

7.3.5 Prior Medications

Prior medications, defined as medications other than study medications which are taken prior treatment start (i.e., prior to the first day of study therapy) other than those anti-cancer therapy will be coded using the WHO Drug Dictionary.

The following summary table will be provided:

- Prior/current non-study medications (classified by medication classes and generic term)

A by-subject listing will accompany the table.

7.3.6 Prior Cancer Therapy

The following will be summarized by treatment arms as randomized or treated:

Prior anti-cancer therapy:

- Prior Surgery (Yes/No, if Yes: type of surgery from the database)
- Prior Radiotherapy (Yes/No, if Yes: sites of radiotherapy from the database)
- Prior Systemic Cancer Therapy (regimen and setting, best response to most recent regimen [CR/PR vs. SD vs. PD], reason for regimen discontinuation)
- Setting of prior systemic therapy regimen received (adjuvant, metastatic disease, recurrent disease, neo-adjuvant).

7.3.7 Baseline Laboratory

Baseline laboratory will be summarized by treatment arm for all subjects.

7.4 Extent of Exposure

Analyses in this section will be performed in all treated subjects by treatment group as treated.

7.4.1 Administration of Study Therapy

The following parameters will be summarized (descriptive statistics) by treatment arm:

- Time from randomization to first dose of study therapy (0 to 3 days, > 3 to 7, > 7 to 14, > 14 to 21, > 21 to 28, > 28). For Group E, time from enrollment to first dose of study therapy will be considered.

The following parameters will be summarized (descriptive statistics) for each drug within the regimen for different arms:

- Relative dose intensity (%) using the following categories: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%.

- Number of doses received (except for BSC in Group B where the dose is not collected on the CRF).
- Cumulative dose (except for BSC in Group B where the dose is not collected on the CRF).

Duration of treatment will be presented by treatment arm using a Kaplan-Meier curve whereby the last dose date will be the event date for those subjects who are off study therapy. Median duration of treatment will be provided. Subjects who are still on study therapy will be censored on their last dose date. Summary table for the duration of treatment will be also provided.

A by-subject listing of dosing of study medication (record of study medication, infusion details, and dose changes) will be also provided. A listing of batch numbers for nivolumab will also be provided.

Below table summarizes the key parameters used to calculate dosing data.

Summary table to describe the Investigator's Choice Chemotherapy for Group C will be provided.

The summary table to describe the Best Supportive Care will be provided for Group B.

Table 7.4.1-1: Administration of Study Therapy: Definition of Parameters

Group A	**Nivolumab**	**Nivolumab + Bevacizumab / Pemetrexed**	**Bevacizumab / Pemetrexed**
Dosing schedule per protocol	240 mg IV q2 weeks	5 mg/kg IV q3 weeks + 15 mg/kg IV q3 weeks / 500 mg/m^2 IV q3 weeks	15 mg/kg IV q3 weeks /500 mg/m^2 IV q3 weeks
Group B	**Nivolumab**	**Best Supportive Care**	**-----**
Dosing schedule per protocol	240 mg IV q2 weeks	-----	-----
Group C	**Nivolumab**	**Investigator's Choice of Chemotherapy**	**-----**
Dosing schedule per protocol	240 mg IV q2 weeks	See section 6.2 Group C	-----
Group D	**-----**	**Nivolumab + Erlotinib**	**Erlotinib**
Dosing schedule per protocol	-----	240 mg IV q2 weeks + 150 mg QD	150 mg QD
Group E	**-----**	**Nivolumab + Crizotinib**	**-----**
Dosing schedule per protocol	-----	240 mg IV q2 weeks + 250 mg BID	
Dose	Dose (mg) is defined as total dose administered (mg) at each dosing date and is collected on the CRF.	Dose (mg) is defined as total dose administered. Dose administered in mg at each dosing date is collected on the CRF.	
Cumulative Dose	Cum dose (mg) is sum of the doses (mg)	Cum dose (mg) is sum of the doses (mg)	

Table 7.4.1-1: Administration of Study Therapy: Definition of Parameters

	administered to a subject during the treatment period.	administered to a subject during the treatment period.
Duration of treatment	Last dose date - Start dose date + 1	Last dose date - Start dose date + 1
Relative dose intensity (%)	Cum dose (unit) / [(Last dose date - Start dose date + a) x b/a] x 100; where a is the number of days per cycle & b is the number per unit. Values for a & b vary per drug. For example nivolumab at 3 mg/kg every 2 weeks: Cum dose (mg/kg) / [(Last dose date - Start dose date + 14) x 3 / 14] x 100]	

7.4.2 Modifications of Study Therapy

The following analyses will be performed for Group D only.

7.4.2.1 Infusion Interruptions and Rate Changes

Each nivolumab, pemetrexed, paclitaxel, nub-paclitaxel, bevacizumab, carboplatin, docetaxel, gemcitabine infusion can be interrupted and/or the IV infusion rate can be reduced. This information will be retrieved from CRF dosing pages.

The following parameters will be summarized by treatment arm:

- Number of subjects with at least one dose infusion interruption, the reason for interruption, and the number of infusion interruptions per subject.
- Number of subjects with at least one IV infusion rate reduction and the reason for reduction.

In addition, nivolumab infusion time (mean, SD, percentage of patients with infusion <= 30 minute, 30 - < =60 minutes, >60 minutes will also be summarized by treatment arms.

7.4.2.2 Dose Escalations

Dose escalations are not permitted for any study drug except erlotinib, for which the dose may be increased if concomitant use with CYP3A4 inducers or concomitant use with the drugs affecting gastric pH according to the drug label.

7.4.2.3 Dose Reductions

Dose reductions are not permitted for nivolumab and bevacizumab.

Carboplatin, pemetrexed, paclitaxel, nab-paclitaxel, docetaxel, gemcitabine, erlotinib, and crizotinib may have dose reductions with the reason collected on Dose Change/Oral Study Medication CRF.

The reason for dose reduction as reported by the investigator will be tabulated for all instances of dose reduction. A category 'Unknown' will be defined for all reductions with no reason reported by the investigator.

The following will be summarized by treatment arm:

- Number and percentage of subjects with at least one dose reduction and reason of the dose reduction.

[redacted]

7.4.4 Immune modulating medication

See the CA209 Core Safety SAP. Only 100-day safety window will be applied.

7.5 Efficacy

- OS is defined as the time from randomization to the date of death. A subject who has not died will be censored at last known date alive.
- Progression-free survival (PFS) is defined as the time from randomization (start of treatment for Group E) to the date of the first documented tumor progression as determined by the investigator using RECIST 1.1 criteria or death due to any cause. Clinical deterioration in the absence of unequivocal evidence of progression (per RECIST 1.1) is not considered progression for purposes of determining PFS. Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who 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 the date they were randomized. Subjects who received any subsequent anti-cancer therapy (including on-treatment palliative RT of non-target bone lesions or CNS lesions) without a prior reported progression will be censored at the last evaluable tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy.

Table 7.5-1: Censoring Scheme for Primary Definition of PFS

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

- DOR (Duration of Objective Response) 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), as determined by the investigator, or death due to any cause, whichever occurs first. For subjects who neither progress nor die, the duration of objective response will be censored on the date of their last evaluable tumor assessment. Subjects who started any subsequent anti-cancer 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. DOR will be evaluated for confirmed responders (i.e. subjects with confirmed CR or PR) only with measurable disease at baseline.
- Objective response rate (ORR) is defined as the number of subjects whose best objective response (BOR) is a confirmed CR or confirmed PR, as determined by the investigator, divided by the number of randomized (or treated for Group E) subjects. BOR is defined as the best response designation, recorded between the date of randomization and the date of objectively documented progression per RECIST v1.1 or the date of subsequent anticancer therapy, whichever occurs first. For subjects without documented progression 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 recorded up to the time of the initial RECIST 1.1-defined progression. ORR will be evaluated only for subjects with measurable disease at baseline.
- Time to Objective Response (TTR) is defined as the time from randomization to the date of the first confirmed response. TTR will be evaluated for confirmed responders only.
- Disease control rate (DCR) is defined as the number of subjects that achieved a best overall response of CR, PR, or SD, divided by the total number of randomized/enrolled subjects with measurable disease at baseline.

7.5.1 Efficacy Analysis: PFS and OS

The analyses of PFS and OS described below will be performed for all groups.

The distribution of PFS and OS will be compared in two randomized arms via a two-sided (unless otherwise specified), log-rank test stratified by respective stratification factors (see section 7.1.1).

The hazard ratio (HR) and the corresponding 100(1-adjusted α)% CI will be estimated in a stratified Cox proportional hazards model using randomized arm as a single covariate.

The PFS and OS curves for each treatment group will be estimated using the Kaplan-Meier (KM) product-limit method and graphically displayed. Two-sided, 95% confidence intervals for median PFS and OS will be constructed based on a log-log transformed CI for the survivor function S(t)[30] [31]. More specific details on these comparisons are provided in the efficacy analysis sections for each group.

PFS and OS rates at 6, 12, 18, 24, etc. months will also be estimated using KM estimates on the PFS curve for each randomized arm. Minimum follow-up must be longer than time point to generate the rate. Associated two-sided 95% CIs will be calculated using the Greenwood's formula[32] for variance derivation and on log-log transformation applied on the survivor function S(t)[33].

By subject listing of PFS per Investigator will be provided.

By subject listing of OS per Investigator will be provided.

7.5.1.1 Subset Analyses of Progression-Free Survival and OS

The influence of baseline and demographic characteristics on the treatment effect will be explored via exploratory subset analyses for the following factor:

- Age categorization (<65, >=65, >=75 (if sufficient subjects are available))

This analysis will be performed for Group D only.

7.5.1.2 Current status of OS follow-up

Current status of OS follow-up will be summarized in months, by computing the time from "last known alive" date to data cut-off date for all randomized/treated subjects separately. Subjects who have a death event will be considered as current for this analysis.

By-subject listings along with IVRS stratification factor will also be produced to accompany the subject time from last known alive date assessment table for all randomized/treated subjects.

7.5.2 Efficacy Analysis: DOR and ORR

The analyses of DOR and ORR described below will be performed for all groups.

Duration of response in each treatment arm will be estimated using KM product-limit method for subjects who achieve PR or CR. Median values along with two-sided 95% CI will be calculated.

Summary statistics will be computed constructed based on a log-log transformed CI for the survivor function S(t). Summary statistics of time to objective response will be provided for each treatment arm for subjects who achieve PR or CR.

To assess further tumor response kinetics, time to response will be analyzed descriptively for randomized subjects with median coming from the KM estimate.

BOR will be summarized by response category for each treatment arm. ORR will be computed in each treatment arm along with the exact 95% CI using Clopper-Pearson method [33].

Individual subject's best overall response (BOR) will be listed based on response evaluation criteria in solid tumor (RECIST) 1.1. BOR will be evaluated for subjects with measurable disease at baseline for Group A and B. For other Groups, it will be evaluated for all randomized/treated subjects.

To assess consistency of treatment effect on ORR in different subsets, ORR will be computed across the same subsets as defined in the PFS and OS analysis.

Additionally, for Group D only, an estimate of the difference in ORRs and corresponding 95% CI will be calculated using CMH methodology and adjusted by the same stratification factors as for analysis of OS. In addition, the stratified odds ratios (Mantel-Haenszel estimator) between the treatments will be provided along with the 95% CI. The difference will be tested via the Cochran Mantel-Haenszel (CMH) test using a two-sided, 5% α level.

7.5.3 Efficacy Analysis: DCR

The analyses of DCR described below will be performed for Group D.

DCR will be summarized by response category for each treatment arm. DCR will be computed in each treatment arm along with the exact 95% CI using Clopper-Pearson method [34]. An estimate of the difference in DCRs and corresponding 95% CI will be calculated using CMH methodology and adjusted by the same stratification factors as for analysis of OS. In addition, the stratified odds ratios (Mantel-Haenszel estimator) between the treatments will be provided along with the 95% CI. The difference will be tested via the Cochran Mantel-Haenszel (CMH) test using a two-sided, 5% α level.

7.5.4 Subsequent Therapy

The following information pertaining to subsequent therapies will be summarized for all randomized/treated subjects separately by treatment arm for Group D only:

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 agents excluding immunotherapy (approved and investigational) by drug name
- Surgery (limited to: tumor resection, curative; tumor resection, palliative; incisional biopsy; excisional biopsy)
- Radiotherapy
- Any combination of the above

7.6 Safety

All safety data will be summarized and listed for all treated subjects unless otherwise specified. All AEs, SAEs, treatment-related AEs, and treatment-related SAEs will be summarized using the worst grade per NCI CTCAE v4.0 by system organ class and preferred term. Lab abnormalities including hematology, chemistry, liver function, thyroid function, and renal function will be summarized using worst grade per NCI CTCAE v4.0 criteria.

Additionally, subject level listings of death, adverse events, serious adverse events, adverse events leading to discontinuation, immune-mediated adverse events, select adverse events will be provided.

7.6.1 Deaths

See Core Safety SAP. Only 100-day safety window will be applied.

7.6.2 Adverse Events

See Core Safety SAP. Only the following summaries will be provided for the 30-day safety window.

- Overall Summary of Any Adverse Events by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5) presented by SOC/PT. This table will be restricted to events with an incidence greater or equal to 5% in any treatment group.
- Overall Summary of Drug-Related Adverse Events by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5) presented by SOC/PT.

7.6.3 Adverse Events Leading to Discontinuation of Study Therapy

See Core Safety SAP. Only the following summaries will be provided for the 30-day safety window.

- Summary of Adverse Events Leading to Discontinuation by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5) presented by SOC/PT
- Summary of Drug-Related Adverse Events Leading to Discontinuation by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5) presented by SOC/PT

7.6.4 Adverse Events Leading to Dose Modification

Not applicable.

7.6.5 Serious Adverse Events

See Core Safety SAP. Only the following summaries will be provided for the 30-day safety window.

- Summary of Serious Adverse Events by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5) presented by SOC/PT.

- Summary of Drug-Related Serious Adverse Events by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5) presented by SOC/PT.

7.6.6 Select Adverse Events

Unless otherwise specified, analyses will be performed by select AE category. Select AEs and Drug-related select AEs (based on list provided by BMS every 6 months) will be summarized for all treated subjects for Group D. Only 30-day safety window will be applied.

- Summary of Any Select Adverse Events by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5)
- Summary of Drug-Related Select Adverse Events by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5)
- Summary of Any Select Endocrine Adverse Events by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5)
- Summary of Drug-Related Select Endocrine Adverse Events by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5)

7.6.6.1 Incidence of select AE

Not applicable.

7.6.6.2 Time-to onset of select AE

Not applicable.

7.6.6.3 Time-to resolution of select AE

See Core Safety SAP. Only 30-day safety window will be applied.

The analyses of time to resolution of drug related select AE will be conducted for Group D.

7.6.7 Immune-Mediated Adverse Events

Immune-mediated AEs (IMAEs) are specific events occurring within 100 days of the last dose of study drug (which includes pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, Immune-mediated encephalitis, and endocrine abnormalities [adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, hypophysitis and diabetis melitus), regardless of causality, for which subjects received immunosuppressive medication for treatment of the event. The exception to the immunosuppressive medication criteria for IMAEs is endocrine events (hypothyroidism/thyroiditis, hyperthyroidism, hypophysitis, diabetes mellitus, adrenal insufficiency), which are included regardless of treatment since these events are often managed without immunosuppression.

Table below provides a summary of the IMAEs category and their respective Preferred Terms. The table might be updated at the time of analysis.

Table 7.6.7-1: Preferred Terms Included in Analysis of IMAEs to Support Warning and Precautions

IMAE Category	Group	Preferred Terms included under IMAE Category
Pneumonitis		Pneumonitis, Interstitial lung disease, Idiopathic interstitial pneumonia
Diarrhea/Colitis		Autoimmune Colitis, Diarrhea, Colitis, Colitis Ulcerative, Enteritis, Enetrocolitis, Enterocolitis haemorrhagic
Hepatitis		Acute Hepatic Failure, Acute on chronic liver failure, Hepatotoxicity, Hepatitis, Hepatitis acute, Autoimmune Hepatitis, AST Increased, ALT Increased, Bilirubin Increased, Transaminases Increased, Drug-induced Liver Injury, Hepatic Failure, Hyperbilirubinaemia,
Adrenal Insufficiency	Endocrine	Adrenal Insufficiency, Hypothalamic Pituitary Adrenal Axis Suppression, Primary adrenal insufficiency, Secondary Adrenocortical Insufficiency, Adrenocortical insufficiency acute
Hypothyroidism/ Thyroiditis	Endocrine	Atrophic Thyroiditis, Autoimmune Hypothyroidism, Autoimmune Thyroiditis, Hypothyroidism, Primary Hypothyroidism, Silent thyroiditis,Thyroiditis, Thyroiditis acute
Hypothyroidism	Endocrine	Autoimmune Hypothyroidism, Hypothyroidism, Primary Hypothyroidism
Thyroiditis	Endocrine	Atrophic Thyroiditis, Autoimmune Thyroiditis, Thyroiditis, Thyroiditis Acute, Silent thyroiditis
Diabetes Mellitus	Endocrine	Diabetes Mellitus, Diabetic ketoacidosis, Fulminant Type 1 Diabetes Mellitus, Latent Autoimmune Diabetes in Adults, Type 1 Diabetes Mellitus, Diabetic ketosis
Nephritis and renal dysfunction		Acute Kidney Injury, Autoimmune Nephritis, Blood Creatinine Increased, Creatinine Renal Clearance Decreased, Hypercreatininaemia, Nephritis, Nephritis Allergic, Paraneoplastic Glomerulonephritis, Renal Failure, Renal Tubular Necrosis, Tubulointerstitial Nephritis
Rash		Autoimmune Dermatitis, Dermatitis, Dermatitis allergic, Dermatitis Exfoliative, Drug Eruption, Erythema Multiforme, Exfoliative Rash, Fixed eruption, Nodular Rash, Pemphigoid, Pemphigus, Rash, Rash Erythematous, Rash Generalised, Rash Macular, Rash Maculo-Papular, Rash morbilliform, Rash Papular, Rash Pruritic, Rash vesicular, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, Toxic skin eruption
Hypersensitivity		Anaphylactic Reaction, Anaphylactic Shock, Hypersensitivity, Infusion Related Reaction
Hyperthyroidism	Endocrine	Basedow's Disease, Hyperthyroidism, Primary Hyperthyroidism
Hypophysitis	Endocrine	Hypophysitis, Hypopituitarism, Lymphocytic Hypophysitis

IMEAs = immune-mediated adverse events

The analysis of IMAEs will be done separately for endocrine IMAEs and IMAEs where immune-modulating medication was initiated.

7.6.7.1 Incidence of IMAEs

See Core Safety SAP. Only 100-day safety window will be applied. Following summaries will be provided.

Summary of Immune-Mediated Adverse Events by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5) Where Immune Modulating Medication Was Initiated by Category with Extended Follow-Up

Summary of Endocrine Immune-Mediated Adverse Events by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5) with Extended Follow-Up

7.6.8 Clinical laboratory evaluations

See Core Safety SAP. Only 30-day safety window will be applied.

[redacted]

7.8 Outcomes Research Analyses

7.8.1 Eligible population

The analysis of FACT-L and EQ-5D will be performed for Group C in all randomized patients who have a screening/baseline assessment and at least 1 follow-up assessment depending on sample size at the data base lock. Same analysis may be performed for Group D.

The questionnaire completion rate for the FACT-L and the EQ-5D, defined as the proportion of questionnaires received out of the expected number (i.e., the number of patients still on treatment in follow-up), will be calculated and summarized at each assessment time point.

7.8.2 FACT-L questionnaire

The FACT-L, including its subscales, will be scored using a 5-point Likert scale (0 = not at all; 1 = a little bit, 2 = somewhat; 3 = quite a bit; 4 = very much). The general subscales include physical well-being (PWB), social/family well-being (SWB), emotional well-being (EWB), and functional well-being (FWB). The seven-item Lung Cancer Subscale (LCS) assesses the impact of symptoms commonly reported by lung cancer patients, including shortness of breath, loss of weight, and chest tightness. A Trial Outcome Index (TOI) can be derived by adding scores on the PWB and FWB subscales to the LCS. The ranges of possible total scores are 0 - 136 for the FACT-L, 0 - 28 for the LCS and 0 - 84 for the TOI, with a higher score representing better quality of life, improved symptomatology and enhanced physical/ functional outcomes, respectively. According to Functional Assessment of Chronic Illness Therapy (FACIT) scoring guidelines [21], in the event of missing responses for some of the questions/ items, scores will be prorated using the average of the other answers in that scale.

The overall FACT-L will be analyzed using descriptive statistics in each treatment arm of the study at each of the assessment time points. Summary statistics including the reporting of means, medians, ranges and standard deviation will be calculated at each assessment point for both categorical and continuous variables.

Baseline and change from baseline of the FACT-L scores at each assessment point will be summarized using descriptive statistics

A determination of whether the 'change' between assessments is clinically meaningful will be assessed by the minimally importance difference (MID) [35] for the FACT-L as validated through published literature. An MID is the "smallest difference in score in the domain of interest that patients perceive as important, either beneficial or harmful, and that would lead the clinician to consider a change in the patient's management [36].

A more detailed description of the FACT-L analyses and results may be presented separately in an independent PRO-Health Economics SAP.

7.8.3 EQ-5D-3L questionnaire

EQ-5D-3L is a standardized measure of self-reported health status. The EQ-5D-3L consists of the EQ-5D-3L five dimension three-level scale descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D-3L descriptive system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: "no problems", "some problems" and "severe problems", which are scored as 1, 2 and 3, respectively. Note that these numerals do not have arithmetic properties and cannot be used as an ordinal scale. Nevertheless, the EQ-5D-3L descriptive system will be converted into EQ-5D-3L index score which provides a measure of health on a scale of 0 to 1 (0 = death and 1 = perfect health).

The EQ VAS records the respondent's self-rated health on a vertical VAS where the endpoints are labeled 'best imaginable health state' (equivalent to a score of 100) and 'worst imaginable health state' (score of zero). This information can be used as a quantitative measure of health outcome as judged by the individual respondents.

Subject's overall health state on a visual analog scale (EQ-VAS) at each assessment time point will be summarized using descriptive statistics (N, mean, SD, median, 25th and 75th percentiles) by treatment arm, as randomized.

Proportion of subjects reporting problems for the five EQ-5D-3L dimensions at each assessment time point will be summarized by level of problem and by treatment arm, as randomized. Percentages will be based on number of subjects assessed at assessment time point.

A by-subject listing of EQ-5D-3L with the problem levels for each of the five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), health state (five dimensions digits combined in a 5-digit number) and EQ-VAS will be provided.

Baseline and change from baseline of the EQ-5D-3L scores at each assessment point will be summarized using descriptive statistics.

A determination of whether the 'change' between assessments is clinically meaningful will be assessed by the minimally importance difference (MID) [35] for the EQ-5D-3L as validated through published literature [37].

A more detailed description of the EQ-5D-3L analyses and results may be presented separately an in an independent PRO-Health Economics SAP.

7.8.3.1 Calculation of Total Scores for Scales/Items

U.S. Population-based EQ-5D-3L Index Score The EQ-5D-3L descriptive system will be converted into an index score which provides a measure of health on a scale of 0 to 1 (0 = death and 1 = perfect health) using the scoring algorithm based on the modeling work[39]:

X = 1 - 0.146016*MO2 - 0.557685*MO3 - 0.1753425*SC2 - 0.4711896*SC3 - 0.1397295*UA2 - 0.3742594*UA3 - 0.1728907*PD2 - 0.5371011*PD3 - 0.156223*AD2 - 0.4501876*AD3 + 0.1395949*D1 - 0.0106868*I2^2 + 0.1215579*I3 + 0.0147963*I3^2,

where

- MO2, SC2, UA2, PD2, and AD2 are dummy variables for level 2 in dimensions mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, respectively;
- MO3, SC3, UA3, PD3, and AD3 are dummy variables for level 3 in dimensions mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, respectively;
- D1 is an ordinal variable: the number of movements away from Full health (level 1) beyond the first (i.e. it takes on values ranging from 0 to 4);
- I2 is an ordinal variable: the number of dimensions at level 2 beyond the first;
- I3 is an ordinal variable: the number of dimensions at level 3 beyond the first.

7.8.4 Handling of Missing Data

For FACT-L, if at least 50% of items within a subscale are completed, each missing item will be imputed by the average of the completed items; if more than 50% of items within a subscale are missing, the score of the subscale will be treated as missing [38].

The total FACT-L and the TOIs will be scored only if at least 80% of the items for each measure are completed and at least 50% of the items are completed within each of the subscales, where the Total FACT-L is made up of the following subscales: PWB + SWB + EWB + FWB + LCS and the Lung TOI is made up of: PWB + FWB + LCS. As long as these two conditions are satisfied, each missing item within for each subscale will be imputed by the average of the completed items.

Any missing scores in the EQ-5D questionnaire will be considered missing.

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 [22]
- For missing and partial adverse event resolution dates, imputation will be performed as follows:
  - If only the day of the month is missing, the last day of the month will be used to replace the missing day
  - If the day and month are missing or a date is completely missing, it will be considered as missing.

- Missing and partial non-study medication domain dates will be imputed using the derivation algorithm described in 4.3.3 of BMS Non-Study Medication Domain Requirements Specification.[23]

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

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

For 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 will be used:

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

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

Duration (e.g. time-to onset, time-to resolution) will be calculated as follows:

Duration = (Last date - first date + 1)

Last known date alive will be defined based on all appropriate dates collected on the CRF.

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

Safety conventions from Programming are summarized in the core safety SAP [24].

9 CONTENT OF REPORTS

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

11 LIST OF ABBREVIATIONS

AE -- adverse event

ALK -- anaplastic lymphoma kinase

ALT -- alanine aminotransferase

APC -- antigen-presenting cells

AST -- aspartate aminotransferase

AT -- aminotransaminases

AUC -- area under the concentration curve

BID -- twice daily

BMS -- Bristol-Myers Squibb

BOR -- best overall response

BSC -- best supportive care

BP -- blood pressure

BUN -- blood urea nitrogen

C -- Celsius

CBC -- complete blood count

CI -- confidence interval

CLS -- capillary leak syndrome

CNS -- central nervous system

CR -- complete response

CRF -- Case Report Form, paper or electronic

CTA -- Clinical Trial Agreement

CTL4-1 -- cytotoxic T-lymphocyte antigen-4

CV -- coefficient of variation

CYP -- cytochrome p-450

DCR -- disease control rate

DILI -- Drug-induced liver injury

DOR -- Duration of response

dL -- deciliter

ECG -- electrocardiogram

ECOG -- Eastern Cooperative Oncology Group

eCRF -- Electronic Case Report Form

EDC -- Electronic Data Capture

EEG -- electroencephalogram

eg -- for example

EGFR -- epidermal growth factor receptor

EQ-5D -- EuroQoL Five Dimension

EWB -- emotional well-being

FACIT – Functional Assessment of Chronic Illness Therapy

FACT-L -- Functional Assessment of Cancer Therapy-Lung

FDA -- Food and Drug Administration

FISH -- fluorescent in-situ hybridization

FSH -- follicle stimulating hormone

FWB -- functional well-being

GCP -- Good Clinical Practice

GI -- gastrointestinal

h -- hour

HBsAg -- hepatitis B surface antigen

HBV -- hepatitis B virus

HCV -- hepatitis C virus

HIV -- human immunodeficiency virus

HR -- hazard ratio

HRQoL -- Health-related Quality of Life

HRT -- hormone replacement therapy

HUS -- hemolytic uremic syndrome

ICH -- International Conference on Harmonisation

ie -- that is

IEC -- Independent Ethics Committee

ILD -- interstitial lung disease

IMP -- investigational medicinal products

IND -- Investigational New Drug

IRB -- Institutional Review Board

IHC -- immunohistochemistry

IU -- international units

IV -- intravenous

IVRS -- Interactive Voice Response System

kg -- kilogram

LCS -- Lung Cancer Subscale

LCSS -- Lung Cancer Symptom Scale

LDH -- lactate dehydrogenase

LFT -- liver function test

MET -- metabolic equivalents

MID -- minimally important difference

mg -- milligram

min -- minute

mL -- milliliter

MLR -- mixed lymphocyte reaction

mmHg -- millimeters of mercury

MVPA -- moderate to vigorous physical activity

MTD -- maximum tolerated dose

mut -- mutation

N -- number

N/A -- not applicable

NIMP -- non-investigational medicinal products

NSAID -- nonsteroidal anti-inflammatory drug

NSCLC -- non-small cell lung cancer

NSQ -- non-squamous

ORR -- objective response rate

OS -- overall survival

PD -- progressive disease

PD-1 -- programmed death-1

PD-L1 -- programmed death- ligand 1

PK -- pharmacokinetics

PFS -- Progression free survival

PO -- oral

PPK -- population pharmacokinetic

PR -- partial response

PRES -- posterior reversible encephalopathy syndrome

PRO -- Patient-reported Outcomes

PS -- performance status

PWB – physical well-being

QD -- once daily

QOL – quality of life

RBC -- red blood cell

RCC -- renal cell carcinoma

SAE -- serious adverse event

SAP -- statistical analysis package

SD -- standard deviation

SED -- sedentary time

SOC -- standard of care

SPP – survival post-progression

SQ -- squamous

SWB – social/family well-being

TCR -- T-cell receptor

T-HALF -- half life

TILs -- tumor-infiltrating lymphocytes

TKI -- tyrosine-kinase inhibitor

TOI -- trial Outcome Index

TTO -- time to trade-off

ULN -- upper limit of normal

VAS -- visual analog rating scale

VEGF -- vascular endothelial growth factor

WBC -- white blood cell

WHO -- World Health Organization

WOCBP -- women of childbearing potential

wt -- wild-type/mutation negative/

12 CHANGES FROM PROTOCOL

- ORR and Duration of Response (DOR): will be evaluated in subjects with measurable disease at baseline.
- Table 7.6.7-1 summary of the IMAEs category and their respective Preferred Terms has been updated with additional terms.

APPENDIX 1 SELECT ADVERSE EVENTS DEFINITION AND CONVENTIONS

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

The final list used for the clinical study report will be included in an Appendix of the CSR.

Time-to onset definition

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

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

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

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

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

Time-to resolution definition

In order to derive the time-to resolution, overlapping or contiguous select AEs within a specific category (defined in Core Safety SAP Table 11-3) will be collapsed into what will be termed "clustered" select AEs. For example, if a subject (without pre-treatment AE) experienced an AE from 1st to 5th January, another AE (with different PT but within same category) from 6th to 11th January and same AE from 10th to 12th January, these will be collapsed into one clustered select AE from 1st to 12th January. Table 10-1 (or Core Safety SAP Table 11-2) is summarizing key derivation steps for each type of clustered select AEs.

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

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

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

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

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

Table 10-1: Derivation of clustered select AE

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

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

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

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

Please refer to CA209 Core Safety SAP for full detail. **Note:** Table 11-3 from Core Safety SAP might be updated at the time of analysis.