Protocol Number: CA209370
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Clinical Protocol CA209370

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

(CheckMate 370: **CHECK**point pathway and nivolu**MA**b clinical **T**rial **E**valuation **370)**

Revised Protocol Number: 05
Incorporates Amendment 04

Study Director/Medical Monitor

Wen Hong Lin, MD

[redacted]

to partners to which BMS has transferred obligations, eg, a Contract Research Organization (CRO).

Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 05	26-Mar-2018	Incorporates Amendment 04
Amendment 04	26-Mar-2018	1. Closes enrollment for Group D 2. Clarifies of 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 [redacted] 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
Revised Protocol 04	28-Mar-2017	Incorporates Amendment 03
Amendment 03	28-Mar-2017	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 03	28-Sep-2016	1. To updates the Adverse Event Management Algorithms for nivolumab per Investigator Brochure Version 15 & Erratum 01 to Investigator Brochure Version 15 2. To update the Study Director/Medical Monitor 3. To address inconsistencies/errors 4. To add cisplatin as one of platinum-based chemotherapies for consistence and for flexibility for the induction therapy 5. The adverse event collection for Group B, Arm B (Best Supportive Care) was updated to commerce at randomization for clarification and consistence 6. To clarify information from the previous version
Revised Protocol 02	29-Oct-2015	Incorporates Administrative Letter 01
Administrative Letter 01	29-Oct-2015	Addresses inconsistencies in the previous version
Revised Protocol 01	31-Jul-2015	Incorporates Amendment 01

Document	Date of Issue	Summary of Change
Amendment 01	31-Jul-2015	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 [redacted]
Original Protocol	15-May-2015	

SYNOPSIS

Clinical Protocol CA209370

Protocol Title: 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

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Nivolumab (Opdivo®) administered IV either alone or in combination with other agents according to the groups assignments are shown below:

Group A: Maintenance following an initial course (4-6 cycles) of investigator's choice of platinum-based chemotherapy, NSQ, PS 0-1, EGFRwt and ALKwt	• **Arm A1: bevacizumab 15 mg/kg q 3 weeks** • **Arm A2: bevacizumab 15 mg/kg + nivolumab 5 mg/kg IV over 30 ± 5 mins q 3 weeks** • **Arm A3: nivolumab 240 mg IV over 30 ± 5 mins q 2 weeks** • **Arm B1: pemetrexed 500 mg/m^2 q 3 weeks** • **Arm B2: pemetrexed 500 mg/m^2 q 3 weeks + nivolumab 5mg/kg q 3 weeks over 30 ± 5 mins** • **Arm B3: nivolumab 240 mg IV over 30 ± 5 mins q 2 weeks**
Group B: Maintenance following an initial course (4-6 cycles) of investigator's choice of standard of care chemotherapy, SQ, PS 0-1	• **Arm A: Nivolumab 240 mg IV over 30 ± 5 mins q 2 weeks** • **Arm B: Best Supportive Care (BSC)**
Group C: First-line, NSQ and SQ, PS 2, EGFRwt and ALKwt	• **Arm A (NSQ):** – **Carboplatin AUC =6 + nab-paclitaxel 100mg/m^2 Days 1, 8, and 15 q 3 weeks** – **Carboplatin AUC = 6 + paclitaxel 200 mg/m^2 q 3 weeks** – **Carboplatin AUC = 6 + pemetrexed 500 mg/m^2 q 3 weeks** – **Carboplatin AUC = 6 + docetaxel 75 mg/m^2 q 3 weeks** – **Paclitaxel 175-225 mg/m^2 q 3 weeks** – **Docetaxel 60-75 mg/m^2 q 3 weeks** – **Gemcitabine 1000 mg/m^2 Days 1 and 8 q 3 weeks** – **Pemetrexed 500 mg/m^2 q 3 weeks** • **Arm A (SQ):** – **Carboplatin AUC =6 + nab-paclitaxel 100mg/m^2 Days 1, 8, and 15 q 3 weeks** – **Carboplatin AUC = 6 + paclitaxel 200 mg/m^2 q 3 weeks** – **Carboplatin AUC = 5 + gemcitabine 1000 mg/m^2 Days 1 and 8 q 3 weeks** – **Carboplatin AUC = 6 + docetaxel 75 mg/m^2 q 3 weeks** – **Paclitaxel 175-225 mg/m^2 q 3 weeks** – **Docetaxel 60-75 mg/m^2 q 3 weeks** – **Gemcitabine 1000 mg/m^2 Days 1 and 8 q 3 weeks** • **Arm B (SQ or NSQ):** – **Nivolumab 240 mg IV over 30 ± 5 mins q 2 weeks**
Group D: First-line, PS 0-2, EGFRmut	• **Arm A: erlotinib 150 mg QD** • **Arm B: nivolumab 240 mg IV over 30 ± 5 mins q 2 weeks + erlotinib 150 mg QD**
Group E: First-line, PS 0-2, ALK-positive	• **Nivolumab 240 mg IV over 30 ± 5 mins q 2 weeks plus crizotinib 250 mg BID**

ALK=anaplastic lymphoma kinase, AUC=Area under the concentration curve; BID=twice a day; EGFR=epidermal growth factor receptor; mins=minutes; mut=mutation; NSQ=non-squamous; PS=performance status; q=every; QD=every day; SQ=squamous; WT=wild-type.

Study Phase: Phase 1/2

Research Hypothesis: The administration of nivolumab monotherapy or nivolumab in combination with standard of care (SOC) therapies to recurrent locally advanced or Stage 4 NSCLC subjects will provide clinical benefit (ie, progression-free survival [PFS], overall survival [OS], and duration of response [DOR] without unacceptable toxicity).

Objectives:

	Primary Objectives	**Secondary Objectives**
Group A: Maintenance, NSQ, PS 0-1, $EGFR_{wt}$ and ALK_{wt}	To compare PFS and OS 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)	• 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)
Group B: Maintenance, SQ, PS 0-1	To compare PFS and OS of maintenance treatment with single agent nivolumab versus best supportive care (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}	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
Group E: First-line, PS 0-2, ALK-positive	To assess the incidence of treatment (nivolumab + crizotinib) related AEs leading to both study drugs discontinuation	• To describe PFS of combination therapy • To assess ORR associated with combined nivolumab and crizotinib therapy

AE=adverse events; ALK=anaplastic lymphoma kinase, BSC=best supportive care; DOR=duration of response; EGFR=epidermal growth factor receptor; mut=mutation; NSQ=non-squamous; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PS=performance status; SQ=squamous; WT=wild-type.

[redacted]

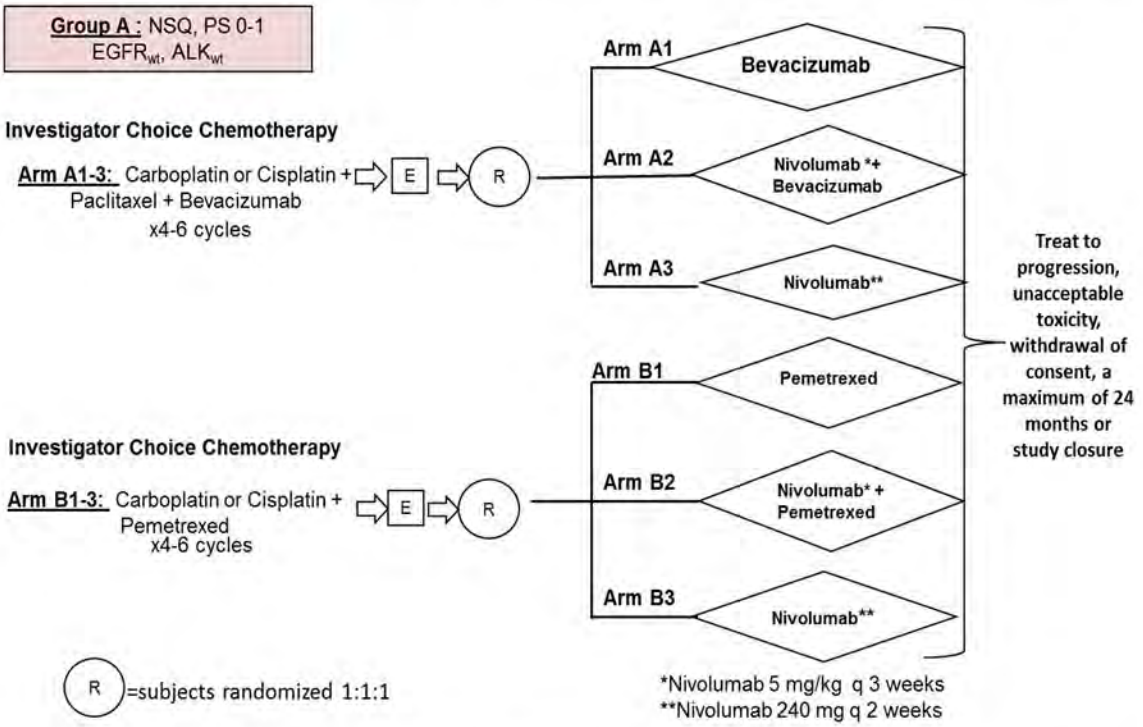
Study Design: This is an open-label, Phase 1/2, Master Protocol containing 5 sub-studies, that will each enroll a unique patient population. Subjects with recurrent locally advanced or Stage 4 SQ or NSQ NSCLC, with an ECOG Performance Status (PS) of 0-2, will receive either first-line or maintenance therapy with nivolumab as a single-agent or in combination with SOC therapies. Subjects will be assigned to treatment groups based on histology, PS, and mutation status to the one of the following five groups:

Note: As per Amendments 03 and 04, Groups A, B, C, and D have closed enrollment and Group E was permanently terminated.

Group A: Maintenance, NSQ PS 0-1, $EGFR_{wt}$ and ALK_{wt}	Group B: Maintenance, SQ, PS 0-1	Group C: First-line NSQ and SQ, PS 2, $EGFR_{wt}$ and ALK_{wt}	Group D: First-line, PS 0-2, $EGFR_{mut}$	Group E: First-line, PS 0-2, ALK-positive

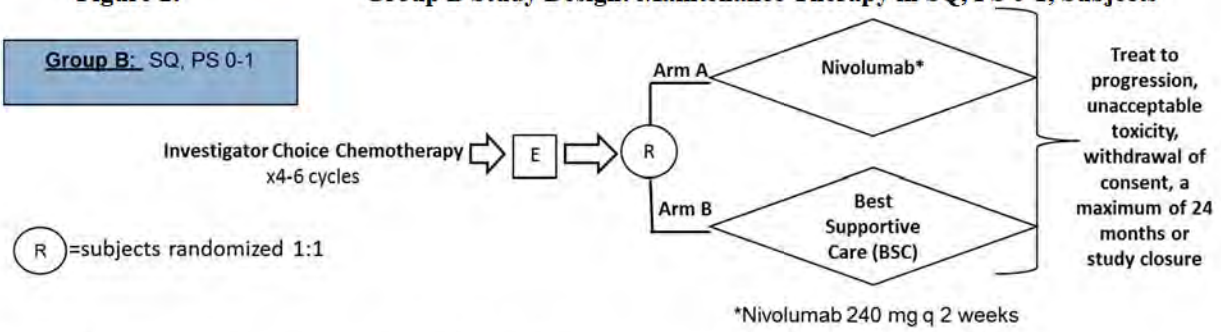
ALK=anaplastic lymphoma kinase; EGFR=epidermal growth factor receptor; mut=mutation; NSCLC=non-small cell lung cancer; NSQ=non-squamous carcinoma; SQ=squamous cell carcinoma; wt=wild-type.

Figure 1: Group A Study Design: Maintenance Therapy in NSQ, PS 0-1, EGFRwt, ALKwt Subjects



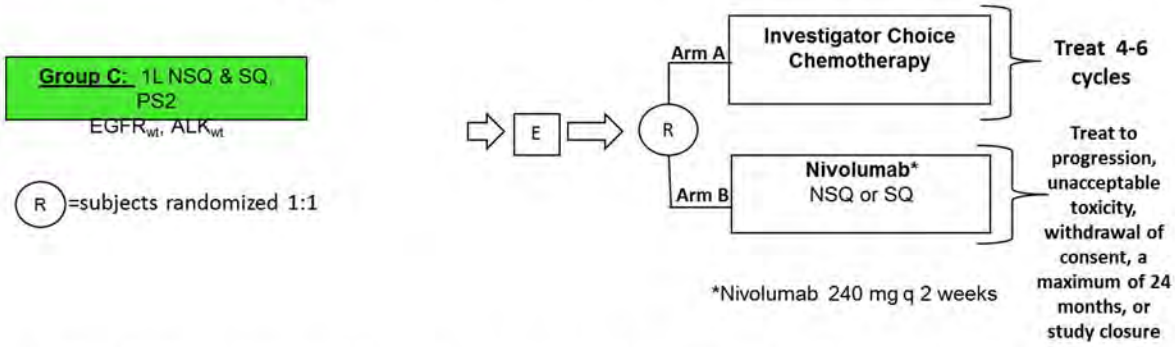
ALK=anaplastic lymphoma kinase; E=enrolled, EGFR=epidermal growth factor receptor; NSQ=non-squamous histology; PS=performance status; R=randomized, q=every; wt=wild-type.

Figure 2: Group B Study Design: Maintenance Therapy in SQ, PS 0-1, Subjects



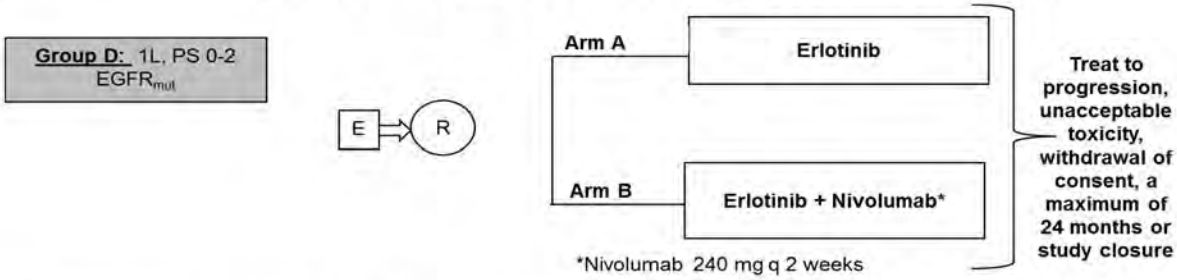
E=enrolled, PS=performance status; R=randomized, SQ=squamous histology; q=every;

Figure 3: Group C Study Design: First-line Therapy in NSQ or SQ, PS 2, EGFRwt, ALK wt Subjects



1L=first line; ALK=anaplastic lymphoma kinase; E=enrolled, EGFR=epidermal growth factor receptor; NSQ=non-squamous histology; PS=performance status; R=randomized, q=every; SQ=squamous histology; wt=wild-type.

Figure 4: Group D Study Design: First-line Therapy in PS 0-2, EGFRmut Subjects



1L=first line; EGFR=epidermal growth factor receptor; E=enrolled; PS=performance status; R=randomized; q=every.

Figure 5: **Group E Study Design: First-line Therapy in PS 0-2, ALK-positive Subjects**

1L=first line; ALK=anaplastic lymphoma kinase; E=enrolled; PS=performance status; q=every.

Study Population: Males and Females, ≥18 years of age, meeting the following criteria:

Note: As per Amendments 03 and 04, Groups A, B, C, and D have closed enrollment and Group E was permanently terminated.

Table 1: **Key Inclusion (see Section 3.3.1 for full inclusion criteria in specific section)**

Group A:	Group B:	Group C:	Group D:	Group E:
• Histologically confirmed recurrent locally advanced or Stage 4 NSQ NSCLC • ECOG PS 0-1 • EGFRwt • ALKwt • Completed 4-6 cycles of bevacizumab or pemetrexed containing induction chemo therapy with no evidence of disease progression	• Histologically confirmed recurrent locally advanced or Stage 4 SQ NSCLC • ECOG PS 0-1 • Completed 4-6 cycles of investigator choice induction chemo therapy with no evidence of disease progression	• Histologically confirmed recurrent locally advanced or Stage 4 SQ or NSQ NSCLC • ECOG PS 2 • EGFRwt • ALKwt	• Histologically confirmed recurrent locally advanced or Stage 4 NSCLC • ECOG PS 0-2 • EGFRmut	• Histologically confirmed recurrent locally advanced or Stage 4 NSCLC • ECOG PS 0-2 • ALK-positive

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

General Exclusion Criteria: Please also see Section 3.3.2 for details of exclusion criteria for each sub-study.

Subjects with untreated CNS metastases are excluded. Exception: Subjects are eligible if CNS metastases are treated and subjects are neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to enrollment. In addition, subjects must be either off corticosteroids, or on a stable or decreasing dose of < 10 mg daily prednisone (or equivalent).

- Subjects with carcinomatous meningitis.
- Subjects with active, known or suspected autoimmune disease. Exceptions: subjects with Type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
- Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone or equivalent) or other immunosuppressive medications within 14 days of first dose of study drug. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

- Subjects with a history of interstitial lung disease (eg, sarcoidosis) that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity. Exception: subjects with chronic obstructive pulmonary disease (COPD) whose disease is controlled at study entry are allowed.
- Subjects with previous malignancies (except non-melanoma skin cancers, and in situ cancers such as the following: bladder, gastric, colon, cervical/dysplasia, melanoma, or breast) are excluded unless a complete remission was achieved at least one years prior to study entry AND no additional therapy is required or anticipated to be required during the study period with the exception of anti-estrogen/androgen therapy or bisphosphonates. Subjects with other active malignancy requiring concurrent intervention are excluded.
- All toxicities attributed to prior anti-cancer therapy other than alopecia, or fatigue, or peripheral neuropathy must be ≤ Grade 1 (NCI CTCAE version 4) before administration of study drug.
- Peripheral neuropathy ≥ Grade 2 (NCI CTCAE version 4)
- Subjects must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before the first dose of study treatment.
- Acute or chronic infection of Hepatitis B or Hepatitis C. Known history of testing positive for Human Immunodeficiency Virus (HIV) or Acquired Immunodeficiency Syndrome (AIDS)

Study Assessments: OS and PFS are co-primary endpoints for Groups A through C, PFS is the primary endpoint for Group D, and the rate of study drugs (nivolumab + crizotinib) discontinuation due to treatment related AEs is the primary endpoint in Group E. Survival endpoints will be assessed as:

- 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 (per RECIST v1.1), as determined by investigators in all Groups, or death due to any cause, whichever occurs first.
- In Group E, PFS and OS are defined as the time of first dose to the date of event since there will be no randomization in this group.
- 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 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.

On study assessments according to RECIST 1.1 criteria will be assessed beginning Week 9 (± 1 week), then every 8 weeks (± 1 week) for up to 2 years as described in Section 5.4 of the protocol until disease progression, death or lost to follow-up. Subjects receiving nivolumab beyond investigator-assessed progression must also continue tumor assessments until such treatment has been discontinued (see Section 4.5.14).

Per Amendment 03, Group E subjects will proceed to follow-up or survival follow up phase. Group E subjects in the follow up phase will require twice weekly liver function monitoring within 60 days of the last dose of nivolumab, followed by once weekly liver function testing 61 through 100 days post last nivolumab dose. Any subject with an abnormal result on liver function testing, within 100 days of last nivolumab dose, will require twice weekly monitoring.

Statistical Considerations: The overall population randomized or enrolled in this Master Protocol was approximately 1953 subjects at maximum. Individual sample sizes and primary endpoints per sub-study are shown in the table below.

Population	Maximum Sample Size	Primary Endpoint	Comparisons of interest
Group A: Maintenance, NSQ, PS 0-1, $EGFR_{wt}$ and ALK_{wt}	765	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	PFS/OS	Nivolumab vs. Best supportive care
Group C: First-line, NSQ and SQ, PS 2, $EGFR_{wt}$ and ALK_{wt}	350	PFS/OS	Nivolumab vs. Investigator choice chemotherapy for superiority and non-inferiority
Group D: First-line, PS 0-2, $EGFR_{mut}$	318	PFS	Nivolumab plus Erlotinib vs. Erlotinib
Group E: First-line, PS 0-2, ALK-positive	20	Incidence of treatment-related AEs leading to discontinuation of both nivolumab and crizotinib	Not Applicable

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

Note: As per Amendments 03 and 04, Groups A, B, C, and D have closed enrollment and Group E was permanently terminated.

Actual samples sizes for study Groups after closed enrollment are listed below:

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

The overall population randomized or enrolled in this Master Protocol is now approximately 342 subjects.

Statistical Analysis

The OS curves for each treatment group will be estimated using the Kaplan-Meier (KM) product-limit method. Two-sided, 95% confidence intervals for median OS will be computed by Brookmeyer and Crowley method.

The subjects may be followed for survival for up to 4 years. Survival rates at 6, 12, 18, 24 months, and up to 4 years will also be estimated using KM estimates on the OS curve for each randomized arm. Associated two-sided 95% CIs will be calculated using the Greenwood's formula.

PFS will be summarized similarly as OS.

ORR will be computed in each treatment group along with the exact 95% CI using the Clopper-Pearson method. BOR will be summarized by response category for each treatment group. A by-subject listing of BOR and tumor measurements will be provided.

All safety data will be summarized and listed for all treated subjects.

Group E primary endpoint of safety analyses:

The number and percentage of subjects who report treatment-related adverse events that lead to study treatment discontinuation will be summarized for all treated subjects. The treatment-related adverse events will be tabulated using worst grade per NCI CTCAE version 4.0 criteria by system organ class and Medical Dictionary for Regulatory Affairs (MedDRA) preferred term. Safety and tolerability is also measured by incidence and severity of AEs and specific laboratory abnormalities in all treated subjects.

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[redacted]

1.3 Objectives

The primary, secondary, and exploratory objectives are summarized in Table 1.3-1.

Table 1.3-1: 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)	[redacted]

Table 1.3-1: Study Objectives

	Primary Objectives	Secondary Objectives
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

[redacted]

Table 1.3-1: 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.

[redacted]

[redacted]

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles

underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol, any amendments, and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

The investigator or BMS should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

2.3 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

BMS will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.

2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4) Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
5) If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed HIPAA Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

Subjects unable to give their written consent (eg, stroke or subjects with or severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this subject become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a subject who is unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is an open-label, Phase 1/2, Master Protocol, 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 treatment groups based on histology, ECOG PS, and mutation status to the one of the following five groups:

- 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 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.

Further details of the design of each Group A through E are provided in Sections 3.1.1 to 3.1.5.

3.1.1 Treatment Group A: Maintenance, NSQ, PS 0-1, $EGFR_{wt}$ and ALK_{wt}

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 4-6 week cycle 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

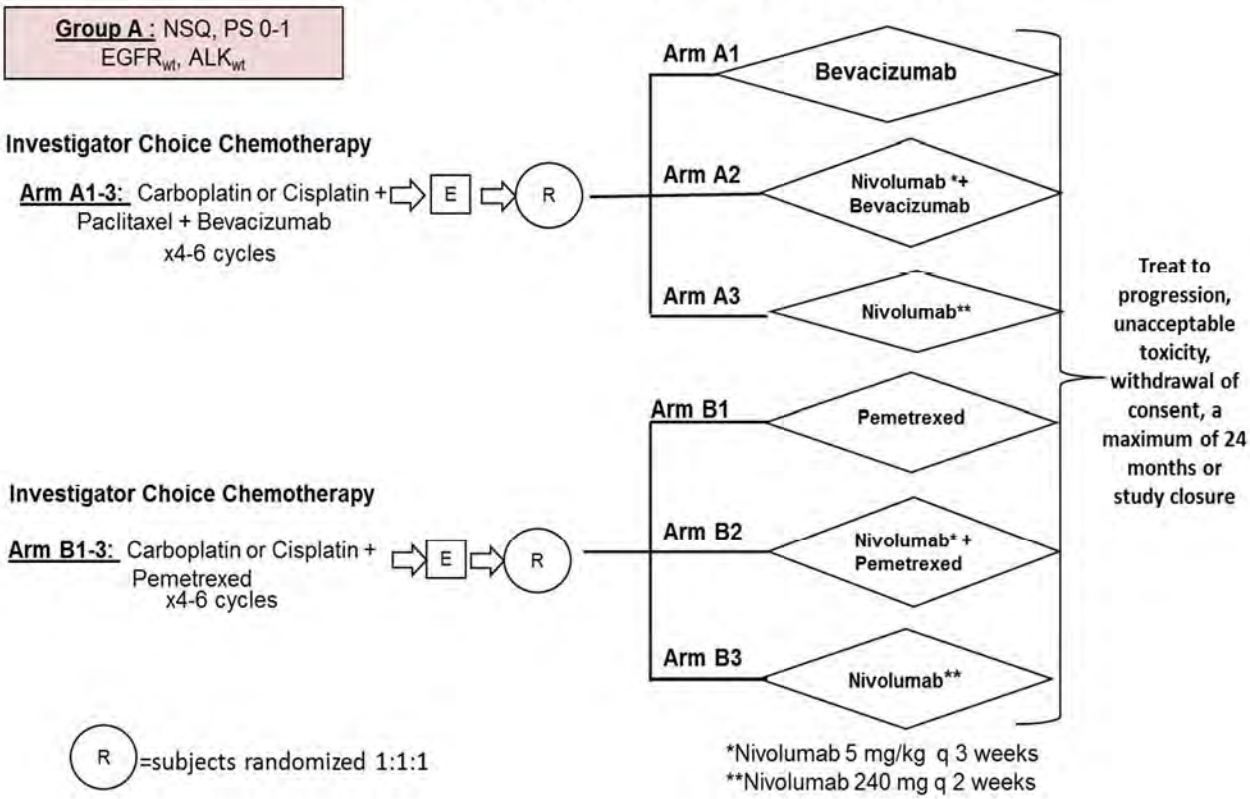
- Arm A3: nivolumab 240 mg every 2 weeks over 30 minute infusion
- Arm B1: pemetrexed 500 mg/m^2 every 3 weeks
- Arm B2: pemetrexed 500 mg/m^2 every 3 weeks + nivolumab 5 mg/kg every 3 weeks over 30 minute infusion
- Arm B3: nivolumab 240 mg every 2 weeks

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 will be performed every 8 weeks (± 1 week) for up to 2 years. The schematic for Group A is presented in Figure 3.1.1-1.

Figure 3.1.1-1: 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; PS=performance status; q=every; R=randomized.

Per Amendment 03 this group is no longer enrolling subjects.

3.1.2 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 will be performed every 8 weeks (± 1 week) for up to 2 years. The Group B schematic is presented in Figure 3.1.2-1.

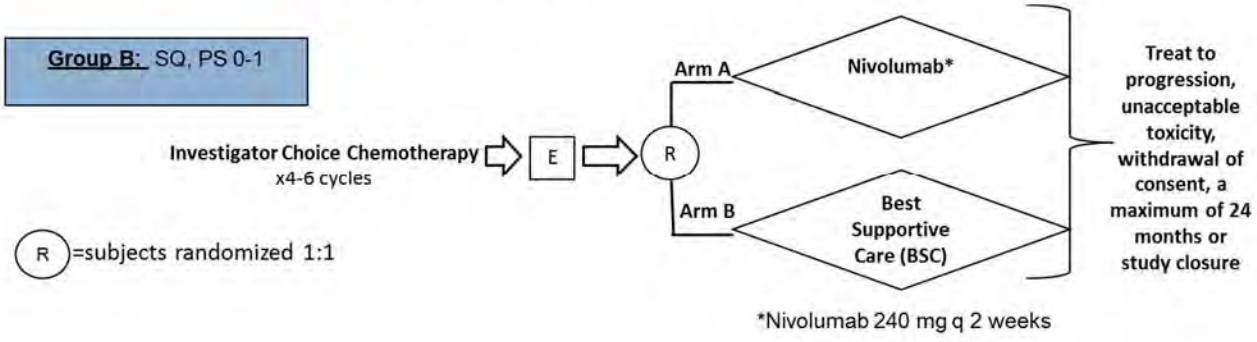
Best supportive care arm may include palliative radiation therapy or palliative surgery. The major components of BSC include:

- Adequate control of pain and other symptoms
- Identification of distressing symptoms
- 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 3.1.2-1: 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; R=randomized; PS=performance status; q=every; SQ=squamous cell carcinoma.

Per Amendment 03 this group is no longer enrolling subjects.

3.1.3 Treatment Group C: First-line, NSQ and SQ, PS 2, $EGFR_{wt}$ and ALK_{wt}

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.

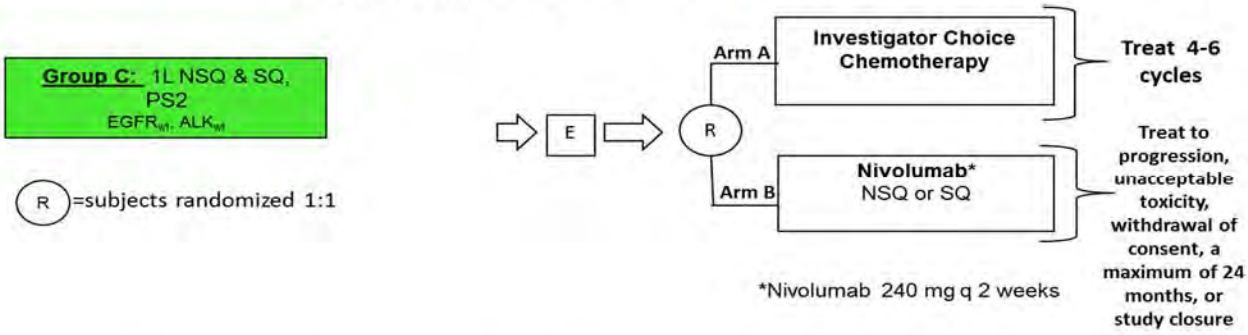
Investigator's Choice chemotherapy regimens will be as follows:

- 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 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
- 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 3.1.3-1.

Figure 3.1.3-1: 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; NSQ=non-small cell carcinoma; R=randomized; PS=performance status; q=every; SQ=squamous cell carcinoma; wt=wild-type.

Per Amendment 03 this group is no longer enrolling subjects.

3.1.4 Treatment Group D: First-line, PS 0-2, $EGFR_{mut}$

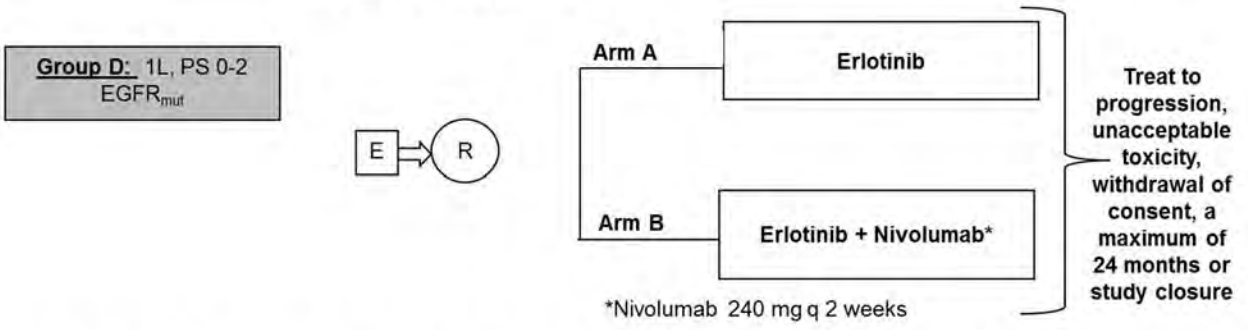
Subjects in Group D will be randomized (1:1) to treatment with erlotinib monotherapy or the combination therapy (erlotinib plus nivolumab) as follows:

- 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 will be performed every 8 weeks (± 1 week) for up to 2 years. The study design schematic is presented in Figure 3.1.4-1.

Figure 3.1.4-1: 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.

3.1.5 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 3.1.5-1. 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 3.1.5-1: 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

A 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.

3.1.6 Enrollment Period

Subjects will be enrolled using an Interactive Web Response System (IWRS). During the screening and enrollment period, a subject will provide signed informed consent and their study eligibility will be established. Additionally, to determine PD-L1 status, tumor tissue (archival or recent tumor biopsy) must be submitted by the site to a third-party vendor.

Subjects are assessed for Group eligibility as described in Section 3.3.

3.1.7 Randomization

Subjects meeting enrollment criteria for Groups A, B, C, or D will be randomized to treatment arms as described in Sections 3.1.1, 3.1.2, 3.1.3, or 3.1.4. An interactive web response system (IWRS) will be utilized for randomization. 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.

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).

3.1.8 Treatment Period

In all treatment groups, treatment will be administered according the dosages and cycles as described in Sections 3.1.1, 3.1.2, 3.1.3, 3.1.4, or 3.1.5.

3.1.9 Study Duration

As per Amendments 03 and 04, enrollment has closed for all groups. The study is expected to end when the last subject in Group D has completed up to 2 years of treatment. The approximate duration of the study is up to 4.5 years. For Group D, the study duration will conclude when the primary analysis takes place. Additional survival analysis may be conducted for up to 4 years after the last subject's start of study treatment, beyond analysis of the primary endpoints.

3.2 Post Study Access to Therapy

At the conclusion of the study, participants who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study treatment for the maximum treatment duration specified in protocol Section 4.5.1. Study treatment will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee, or through another mechanism at the discretion of BMS. BMS reserves the right to terminate access to study drug if any of the following occur: a) the marketing application is rejected by the responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a government sponsored or private health program; or d) therapeutic alternatives become available in the local market.

3.3 Study Population

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria. For entry into the study, the following criteria MUST be met.

Note: as per Amendments 03 and 04, Groups A, B, C, and D have closed enrollment and Group E was permanently terminated.

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

Subjects must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal subject care.

2. Target Population

Table 3.3.1-1: Target Population

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 Consult with the Medical Monitor for eligibility for "wild type" mutations (eg, exon 20)	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 drug-sensitizing mutation (including, but not limited to exon 19 deletion, exon 21-L858R-substition mutation)	e) Negative/wild type, or indeterminate
v. ALK translocation[c]	a) Negative/wild type, or indeterminate	b) Primary SQ histology tumors are not required to be tested for ALK translocation	c) Negative/wild type, or indeterminate. Primary SQ histology tumors are not required to be tested for ALK translocation	d) Negative/Wild type, or indeterminate	e) 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. Subjects in Group A and B with a complete response after his/her induction chemotherapy will not have measureable disease and will be eligible for enrollment.				

Table 3.3.1-1: Target Population

Criterion	Group A	Group B	Group C	Group D	Group E
	b) Groups A and B: Subjects with CR/PR/SD to initial induction therapy are allowed to enroll		c) Not Applicable		
vii. Tissue requirement[d]	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 edition International Association for the Study of Lung Cancer classification, with no prior systemic anticancer therapy (including EGFR and ALK inhibitors) given as primary therapy for advanced or metastatic disease. Prior adjuvant or neoadjuvant chemotherapy is permitted as long as the last administration of the prior regimen occurred at least 6 months prior to disease recurrence. Prior definitive chemoradiation or adjuvant radiotherapy for locally advanced disease is also permitted as long as the last administration of chemotherapy or radiotherapy (whichever was given last) occurred at least 6 months prior to disease recurrence.

[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. Consult the Medical Monitor regarding the use of EGFR/ALK mutation blood tests.

[d] Fine needle biopsies, drainage of pleural effusions with cytospins, or punch biopsies are not considered adequate. Biopsies of bone lesions that do not have a soft tissue component or decalcified bone tumor samples are also not acceptable.

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

3. Age and Reproductive Status

a) Men and women, ≥ 18 years of age.

b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.

c) Women must not be breastfeeding

d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug (s) nivolumab plus 5 half-lives of nivolumab (5 times the half-life=125 days) plus 30 days (duration of ovulatory cycle) for a total of 155 days or 23 weeks post-treatment completion.

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with nivolumab plus 5 half-lives

of the study drug (125 days) plus 90 days (duration of sperm turnover) for a total of 31 weeks post-treatment completion.

f) Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, they must still undergo pregnancy testing as described in this section.

4. Baseline laboratory Parameters

Table 3.3.1-2: Baseline laboratory Parameters (All Groups)

Test	Value
i. WBC	≥ 2000/uL
ii. Neutrophils	≥ 1500/uL
iii. Platelets	≥ 100 x 10^3/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)

ULN=upper limit of normal.

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

3.3.2 Exclusion Criteria

1. Target Population

Table 3.3.2-1: Target Population

Criterion	Group A	Group B	Group C	Group D	Group E
i. EGFR mutation	a) EGFR mutation test was not done for primary adenocarcinoma				
ii. ALK translocation	a) ALK translocations test was not done for primary adenocarcinoma				

Table 3.3.2-1: Target Population

Criterion	Group A	Group B	Group C	Group D	Group E
iii. Subjects with recurrent disease: chemo-therapy and radiotherapy for previous localized disease	Last administration of adjuvant or neoadjuvant chemotherapy, definitive chemoradiation, or adjuvant radiotherapy was < 6 months prior to disease recurrence				
iv. Previous anticancer therapy	a) Induction chemo therapy other than listed regimens (Section 3.1.1 and 3.1.2) are excluded for Groups A and B		b) Any prior systemic therapy for advanced or metastatic disease is excluded for Groups C, D and E.		
v. Progression after initial induction chemotherapy	a) Progression after initial induction chemotherapy for Group A and B subjects		b) Not Applicable		
vi. Radiation therapy	a) Palliative radiation therapy completed < 2 weeks prior to randomization is excluded. Exception: Ablative/definitive radiation therapy to oligometastasis is allowed for Groups A and B before enrollment.* There is no need for a washout period prior to first nivolumab dose. AEs from radiation therapy should resolve to Grade ≤ 1 prior to on study treatment. In addition, subjects must be either off corticosteroids, or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent).				
vii. CNS metastasis	a) Subjects with untreated CNS metastases are excluded. b) Exception: Subjects are eligible if CNS metastases are adequately treated and subjects are neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to enrollment. In addition, subjects must be either off corticosteroids, or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent). c) Subjects with carcinomatous meningitis				

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

* Concurrent ablative/definitive radiation therapy with induction chemotherapy is acceptable for Group A and Group B.

2. Medical History

Table 3.3.2-2: Medical History

Description	Group A	Group B	Group C	Group D	Group E
i. Cardiovascular and Hematologic	a) Not Applicable.				b) Ongoing cardiac dysrhythmias of NCI CTCAE

Table 3.3.2-2: Medical History

Description	Group A	Group B	Group C	Group D	Group E
					Grade ≥ 2, uncontrolled atrial fibrillation of any grade, or QTc interval > 470 msec.
ii. Dermatologic and trauma/surgery	a) Unhealed open wound b) Major surgery or significant traumatic injury within 4 weeks of first on-study treatment is excluded for bevacizumab containing arms. c) Major surgery or significant traumatic injury within 2 weeks of first on-study treatment is excluded for all arms	d) Unhealed open wound e) Major surgery or significant traumatic injury within 2 weeks of first on-study treatment			
	f) Skin disorders requiring chronic systemic steroid treatment are excluded				
iii. Neuropathy	a) Subjects with ≥ Grade 2 peripheral neuropathy are excluded				
iv. Neurologic	a) Untreated or active/progressing CNS metastases are excluded. b) Exceptions: Subjects are eligible if CNS metastases are adequately treated and subjects are neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to enrollment. c) Carcinomatous meningitis				
v. Pulmonary	a) History of interstitial lung disease (eg, sarcoidosis) that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity is excluded. Exception: Subjects with COPD whose disease is controlled at study entry are allowed.				
vi. Malignancy	a) Subjects with previous malignancies (except non-melanoma skin cancers, and in situ cancers such as the following: bladder, gastric, colon, cervical/dysplasia, melanoma, or breast) are excluded unless a complete remission was achieved at least 1 year prior to study entry and no additional therapy is required or anticipated to be required during the study period, with the exception of anti-estrogen/androgen therapy or bisphosphonates.				

Table 3.3.2-2: Medical History

Description	Group A	Group B	Group C	Group D	Group E
	b) Other active malignancy requiring concurrent intervention				
vii. Autoimmune disease	a) Active, known or suspected autoimmune disease (eg, rheumatoid arthritis, multiple sclerosis). b) Exceptions: skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.				
viii. Other	a) Bevacizumab and pemetrexed specific exclusion criteria are per individual agent package insert	b) Best supportive care arm excludes definitive radiation therapy and surgery (other than palliative in nature, chemotherapy, targeted, biologic or immune therapies	c) Chemotherapy specific exclusion criteria are per individual agent package insert	d) Erlotinib specific exclusion criteria are per package insert	e) Crizotinib specific exclusion criteria are per package insert
	f) Group A and B: All toxicities attributed to prior anti-cancer therapy other than alopecia, fatigue, or peripheral neuropathy must have resolved to Grade 1 (NCI CTCAE version 4) or baseline before administration of study drug.		g) Not Applicable		
	h) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS) i) Acute or chronic infection of hepatitis B virus or hepatitis C. j) Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. k) Exceptions: Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease. l) Exceptions: Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement are eligible to enroll.				

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

3. Physical and Laboratory Test Findings

a) Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic infection
b) History of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)
c) Subjects with ≥ Grade 2 peripheral neuropathy
d) Women who are pregnant or breastfeeding

4. Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to platinum-containing compounds or other study drug components

5. Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated
b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness
c) Any other serious or uncontrolled medical disorder, active infection, physical exam finding, laboratory finding, altered mental status, or psychiatric condition that, in the opinion of the investigator, would limit a subject's ability to comply with the study requirements, substantially increase risk to the subject, or impact the interpretability of study results

NOTE: This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, subject has been randomized/enrolled, but has not been treated). If re-enrolled, the subject must be re-consented.

3.3.3 Women of Childbearing Potential

A woman of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40mIU/mL to confirm menopause.

Note: Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels. If the serum FSH level is >40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal:

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months.

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.

NOTE: Partners of male subjects are to use one highly effective method of contraception.

Subjects must agree to use one highly effective contraception methods as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

- Progestogen only hormonal contraception associated with inhibition of ovulation
- Hormonal methods of contraception including oral contraceptive pills (combination of estrogen and progesterone), vaginal ring, injectables, implants, transdermal and intrauterine hormone-releasing systems (IUS)
- Bilateral tubal ligation
- Vasectomized Partner
- Intrauterine devices (IUD)
- Complete abstinence

  *Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

Unacceptable METHODS OF CONTRACEPTION

- Vaginal sponge with spermicide
- Progestin only pills
- Cervical cap with spermicide
- Diaphragm with spermicide
- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicide only
- Lactation amenorrhea method (LAM)
- A male and a female condom must not be used together
- Male condoms with or without spermicide for partners of female subjects, as the only method of contraception.
- Female condoms

[redacted]

3.5 Discontinuation of Subjects following any Treatment with Study Drug

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Subject's request to stop study treatment
- Any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Additional protocol specified reasons for discontinuation or dose modifications (See Sections 4.5.1 thru 4.5.14)

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

For the subjects who are treated with the combination of nivolumab and Standard of Care, if a subject discontinues one of the drugs the subject needs to discontinue the combination treatment.

All subjects who discontinue study drug should comply with protocol specified follow-up procedures as outlined in Section 5. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study drug is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate case report form (CRF) page.

3.6 Post Study Drug Study Follow-up

As the mean terminal elimination half-life of nivolumab is 17 to 25 days, the safety follow-up after discontinuation of nivolumab single-agent dosing will be 100 days, or approximately 5 half-lives. It is recognized that subsequent therapies may be initiated during the 100-day safety follow-up, and investigators will be advised to consider the potential contribution of prior study treatment in addition to the subsequent therapy being administered at the time that any adverse event is observed when assessing causality of the event.

BMS may request that survival data be collected on all treated/randomized participants outside of the protocol-defined window in Section 5. At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contacts or is lost to follow-up.

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study drug will remain in the study and must continue to be followed for protocol specified in end of treatment and follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study, procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

3.6.2 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 STUDY DRUG

Nivolumab 100 mg (10 mg/mL) will be packaged in an open-label fashion. Ten (10) nivolumab 10 mL vials will be packaged within a carton (see Table 4-1). The vials are not subject or treatment group specific although there will be specific vial assignments by subject distributed by the IWRS in order to track drug usage and re-supply.

Study drug includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) and can consists of the following:

Table 4-1: Study Drugs for CA209370

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
Nivolumab Solution for Injection	100 mg (10 mg/mL)	10 mL per vial/ Open-label	5 or 10 vials per carton/ Open-label	Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect from light and freezing
Bevacizumab	100 mg/4 mL (4 mL) [a]	4 ml per vial/open-label	4 ml or 16 ml Open-label	Solution	2–8°C. Protect from light
Carboplatin Solution for Injection	450 mg/vial (10 mg/mL)[a]	45 mL per vial/ Open-label	4 vials per carton/Open-label	Clear, colorless or slightly yellow solution	Store at or below 25°C. Protect from light.
Cisplatin	50 mg/vial, 100 mg/vail (1 mg/mL)	50 mL per vial and 100 mL per vial/ Open-label	1 vial per carton/Open-label	Clear, colorless, sterile aqueous solution	Store at 15°C to 25°C. Protect from light
Crizotinib	Capsules: 250 mg and 200 mg.[a]	Capsules: 250 mg and 200 mg.	Bottles of 60 capsules, Open-label	Capsule of pink opaque cap and body	Store at room temperature 20°C to 25°C
Docetaxel	80 mg/2 mL and 20 mg/0.5 mL[a]	Single-dose vial	In a blister pack in one carton, Open-label	Non-aqueous, viscous solution	Store between 2°C and 25°C
Erlotinib	Tablets: 25 mg, 100 mg and 150 mg	Tablets 25 mg, 100 mg and 150 mg	Bottles of 30 tablets Open-label	white film-coated tablet	Store at room temperature 15°C to 30°C
Gemcitabine Powder for Solution for Infusion	1000 mg/vial[a]	1000 mg per vial/ Open-label	1 vial per carton/Open-label	White to off-white plug or powder	Store at 15-30°C
Pemetrexed Powder for Concentrate for Solution for Infusion	500 mg/vial[a]	500 mg per vial/ Open-label	1 vial per carton/ Open-label	White to either light yellow or green-yellow lyophilized powder	Store at 25°C. Excursions permitted (15-30°C)
Paclitaxel Solution for Injection	100 mg/vial[a] (6 mg/mL)	16.7 mL vial/ Open-label	4 vials per carton/Open-label	Clear, colorless or slightly yellow viscous solution	Store at 15°C-30°C. Protect from light.
Nab-paclitaxel	100 mg in a single use vial[a]	Individually packaged in a carton.	1 vial per carton/Open-label	Lyophilized powder	20°C to 25°C, Protect from bright light.

[a] These products may be obtained by the investigational sites as local commercial product in certain countries if allowed by local regulations. In these cases, products may be a different pack size/potency than listed in the table. These products should be prepared/stored/administered in accordance with the package insert or summary of product characteristics (SmPC).

4.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

Nivolumab is to be administered intravenously (IV) for 30 min ± 5 minutes in this Master Protocol. Investigational product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

Dosing calculation for nivolumab should be based on the body weight assessed as per Table 5.1-1. If the subject's weight on the day of dosing differs by >±10% from the weight used to calculate the prior dose, the dose must be recalculated. All doses should be rounded to the nearest milligram. There will be no dose modifications allowed for nivolumab.

4.2 Non-investigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.

Gemcitabine, pemetrexed, paclitaxel, nab-paclitaxel, carboplatin, bevacizumab, erlotinib, crizotinib, etc. will be procured by the investigator as local commercial product. The sites will also procure IV bags, diluents, and micron in-line filters (ie, 0.2/0.22 micron; see current nivolumab Investigator Brochures for required filter details).

4.3 Storage and Dispensing

The product storage manager should ensure that the study drug (Nivolumab) is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

Study drug not supplied by BMS will be stored in accordance with the package insert.

Investigational product documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

4.4 Method of Assigning Subject Identification

CA209370 is an open-label study. All enrolled subjects will be assigned a subject number, starting with 00001. After it has been determined that the subject meets all eligibility criteria of the study, the investigator (or designee) will register the subject by following the enrollment procedures established by BMS. The following information is required for registration:

- Date of birth
- Gender at birth
- Diagnosis
- Date of informed consent
- Planned date of 1st dose.

The subject number will be assigned through an interactive web response system (IWRS) once the subject signs informed consent. Every subject that signs informed consent must be assigned a subject number in IWRS. Specific instructions for using IWRS will be provided to the investigational site in a separate document. Enrolled subjects meeting all eligibility criteria will be assigned to sub-protocols according to their mutation status, histology subtype and performance status to one of the treatment arms according to their histology subtype and treatment arm availability.

4.5 Selection and Timing of Dose for Each Subject

Subjects will be assigned to one of 5 sub-protocols:

- **Group A (NSQ, Maintenance Therapy):** Single-agent nivolumab, single-agent pemetrexed or bevacizumab, or the combination of nivolumab and pemetrexed or bevacizumab. The treatment arms are:
  - 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/m^2 every 3 weeks
  - Arm B2: pemetrexed 500 mg/m^2 every 3 weeks, plus nivolumab 5 mg/kg every 3 weeks over 30 minute infusion
  - Arm B3: nivolumab 240 mg every 2 weeks over 30 minute infusion

  Nivolumab is to be administered first, bevacizumab or pemetrexed will start at least 30 minutes after completion of the nivolumab infusion.

- **Group B (SQ, Maintenance Therapy)**: Either single-agent nivolumab, or BSC
  - Nivolumab 240 mg, every 2 weeks over 30 minute infusion
  - BSC

- **Group C (First-line, PS 2):** Either Investigator's Choice chemotherapy or single-agent nivolumab as first-line treatment.

  Nivolumab: 240 mg every 2 weeks, OR Investigator's Choice chemotherapy regimens will be as follows:

  - **Arm A** (Investigator's Choice chemotherapy, 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** (Investigator's Choice chemotherapy, 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 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
  - **Arm B** (Nivolumab, SQ or NSQ)

    Nivolumab: (240 mg) every 2 weeks over 30 minute infusion

- **Group D (First-line, EGFR mutation):** First-line treatment with erlotinib or the combination of nivolumab + erlotinib.
  - Arm A: erlotinib (150 mg QD)
  - Arm B: nivolumab (240 mg) every 2 weeks over 30 minute infusion + erlotinib (150 mg QD)

- **Group E (First-line, ALK positive)**: First-line treatment with nivolumab and crizotinib
  - Subjects will receive the combination of nivolumab (240 mg) every 2 weeks over 30 minute infusion and crizotinib (250 mg BID).

All subjects who discontinue study treatment should comply with protocol specified end of treatment and follow-up procedures as outlined in the schedule of events. Subjects will continue with the on-study visit schedule until disease progression following retreatment or upon a decision

to not receive retreatment, unacceptable toxicity, or withdrawal of informed consent. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness). If study treatment is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate CRF page.

4.5.1 Duration of Treatment with Nivolumab for Groups A, B, C, and D

The optimal duration of immunotherapy is currently unknown. However, because immunotherapy engages the immune system to control the tumor, continuous treatment as is required with targeted agents or cytotoxic therapy may not be necessary.

Accumulating evidence from different clinical trials in different tumors types with nivolumab indicates that most of the responses are generally occurring early, with a median time to response of 2-4 months including in subjects with NSCLC,[89,90] and a recent analysis in a melanoma study suggests the majority of subjects who discontinue nivolumab for toxicity maintain disease control in the absence of further treatment.[91]

For these reasons, treatments with nivolumab will be given for up to 24 months in the absence of disease progression or unacceptable toxicity. Chemotherapy will be given as per the study dosing schedule.

With the early closure of groups A, B, C, and D, subjects currently on treatment in these groups 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 subject.

4.5.2 Nivolumab Treatment Discontinuation

Nivolumab treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related AE lasting > 7 days or recurs, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation

- ♦ Grade ≥ 3 drug-related AST, ALT or Total Bilirubin requires discontinuation*
- ♦ Concurrent AST or ALT > 3 x ULN and total bilirubin > 2x ULN

* In most cases of Grade 3 AST or ALT elevation, study treatment will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

- Any Grade 4 drug-related adverse event or laboratory abnormality (including but not limited to creatinine, AST, ALT, or Total Bilirubin), except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 drug-related endocrinopathy adverse events, such as ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor or designee.
- Any event that leads to delay in dosing lasting > 6 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks from the previous dose, the BMS medical monitor or designee must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.
  - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor or designee. Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks, the BMS medical monitor or designee must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.

Subjects will be monitored continuously for AEs while on study. Treatment modifications (eg, dose-delay or discontinuation) will be based on specific laboratory and AE criteria. Early recognition and management may mitigate severe toxicity. Evaluation and Management Guidelines were developed to assist investigators and can be found in the Investigator Brochure and in Appendix 1 of this protocol:

- Suspected Pulmonary Toxicity
- Diarrhea and Colitis
- Suspected Hepatotoxicity (including asymptomatic liver function tests [LFT] elevations)
- Suspected Endocrinopathy
- Nephrotoxicity
- Neurotoxicity

4.5.3 Dose Delay Criteria

Tumor assessments for all subjects should continue as per protocol even if dosing is delayed.

4.5.3.1 Nivolumab Dose Delay Criteria

Nivolumab administration should be delayed for the following:

- Grade ≥ 2 non-skin, drug-related AE, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities
- Any Grade 3 skin, drug-related AE
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay
  - Grade ≥ 3 AST, ALT, Total Bilirubin will require dose discontinuation (see Section 4.5.3.1)
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Participants who require delay of nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab dosing when re-treatment criteria are met.

4.5.3.2 Resumption of Nivolumab

Treatment may resume when the AE(s) resolve(s) to Grade 1 or baseline value. If treatment must be delayed for > 6 weeks from the last dose, please contact the Study Director/Medical Monitor before resuming dosing.

In subjects receiving corticosteroids to treat a drug-related AE, nivolumab may not be resumed until the corticosteroid has been tapered to a dose less than or equivalent to prednisone 10 mg/day.

Tumor assessments for subjects who delay study treatment should continue as per protocol until radiographic progression is assessed by the investigator.

Subjects may resume treatment with nivolumab when the suspected drug-related AE(s) resolve(s) to Grade ≤ 1 or baseline, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Subjects who have not experienced a Grade 3 suspected drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- For subjects with Grade 2 AST, ALT and/or Total Bilirubin Abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.

- Subjects with combined Grade 2 AST/ALT and total bilirubin values meeting discontinuation parameters (see Section 4.5.2) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea or colitis must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by BMS Medical Monitor (or designee).
- Subjects with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor (or designee). Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
- Dose delay of nivolumab which results in treatment interruption of > 6 weeks requires treatment discontinuation, with exceptions as noted in Section 4.5.3.1.

4.5.4 Nivolumab Dose Modifications

There will be no dose reductions for nivolumab.

4.5.5 Bevacizumab Treatment Discontinuation:

Bevacizumab should be discontinued for gastrointestinal perforations, fistula formation involving an internal organ, wound dehiscence and wound healing complications requiring medical intervention, serious hemorrhage, severe arterial thrombotic events, hypertensive crisis or hypertensive encephalopathy, reversible posterior leukoencephalopathy syndrome, or nephrotic syndrome (see Boxed Warning, Warnings and Precautions in the bevacizumab label). Bevacizumab should be held for severe hypertension not controlled with medical management, moderate to severe proteinuria, and severe infusion reactions.

4.5.6 Bevacizumab Dose Modifications

There are no dose modifications for bevacizumab.

4.5.7 Pemetrexed Treatment Discontinuation

Pemetrexed therapy should be discontinued if a subject experiences any hematologic or non-hematologic Grade 3 or 4 toxicity after 2 dose-reductions (except Grade 3 transaminase elevations) or immediately if Grade 3 or 4 neurotoxicity is observed.

4.5.8 Pemetrexed Dose Reductions

If subjects develop nonhematologic toxicities (excluding neurotoxicity) ≥ Grade 3, treatment should be withheld until resolution to less than or equal to the subject's pre-therapy value.

If subjects develop any Grade 3 or 4 toxicities except mucositis, any diarrhea requiring hospitalization (irrespective of Grade) or Grade 3 or 4 diarrhea, the subsequent pemetrexed dose will be reduced by 25%.

If subject develops Grade 3 or 4 mucositis, subsequent pemetrexed dose will be reduced by 50%.

Dose Reduction for Pemetrexed (single-agent or in combination)- Hematologic Toxicities

Pemetrexed dose reductions should follow the guidelines below:

- Nadir ANC < 500/mm^3 and nadir platelets ≥50,000/mm^3, or Nadir platelets < 50,000/mm^3 without bleeding regardless of nadir ANC, subsequent pemetrexed dose will be reduced by 25%.
- Nadir platelets <50,000/mm^3 with bleeding, regardless of nadir ANC, subsequent pemetrexed dose will be reduced by 50%.

In the event of neurotoxicity, therapy should be held until resolution of symptom to ≤ Grade 1. Subjects should discontinue therapy if Grade 3 or 4 neurotoxicity is experienced.

Pemetrexed should not be administered to subjects whose creatinine clearance is < 45 mL/min using the standard Cockcroft and Gault formula (below) or GFR measured by Tc99m-DPTA serum clearance method.

Growth factors are permissible to allow for hematological recovery. Please use local standards of care in the use of these supportive measures. Additionally, the use of prophylactic dose antibiotics is to be used according to local standards of care. Please note any antibiotic or growth factor use on the eCRF.

4.5.9 Group C: Investigator's Choice Chemotherapy Dose Discontinuation:

Except where specified below, both chemotherapy drugs in the investigator's choice chemotherapy regimen should be discontinued for any of the following:

- Any Grade ≥ 3 peripheral neuropathy
- Grade ≥ 3 drug-related thrombocytopenia associated with clinically significant bleeding
- Any drug-related liver function test (LFT) abnormality that meets the following criteria requires discontinuation:
  - AST or ALT > 5-10 ×ULN for > 2 weeks
  - AST or ALT > 10 ×ULN
  - Total bilirubin > 5 ×ULN
  - Concurrent AST or ALT > 3 ×ULN and total bilirubin > 2 ×ULN
- Any drug-related AE which recurs after two prior dose reductions for the same drug-related AE requires discontinuation of the drug(s) which was/were previously dose reduced.
- Any Grade ≥ 3 drug-related hypersensitivity reaction or infusion reaction requires discontinuation of the drug(s) felt to be causing the reaction. The drug not felt to be related to the hypersensitivity reaction or infusion reaction may be continued.
- Any Grade 4 drug-related AE which the investigator deems is inappropriate to be managed by dose reduction(s) requires discontinuation of the drug(s) felt to be causing the event. The drug not felt to be related to the event may be continued.
- Any event that leads to delay in dosing of any study drug(s) for > 6 weeks from the previous dose requires discontinuation of that drug(s) with the following exception:
  - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor or designee. Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks, the BMS medical monitor or designee must be consulted. Periodic study visits to assess safety and laboratory

studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued investigator's choice chemotherapy dosing. Investigators should consult local labeling for the chemotherapy drugs being administered to any given subject for additional guidance on dose discontinuation.

4.5.10 Group C: Investigator's Choice Chemotherapy Dose Reductions

Dose reductions of Investigator's Choice chemotherapy may be required, and will be performed according to Table 4.5.10.1-1. Chemotherapy dose reductions are permanent; once the dose of any chemotherapy agent is reduced, it may not be re-escalated in subsequent cycles. The dose reductions for each agent in the Investigator's Choice chemotherapy regimen are not linked and may be adjusted independently.

4.5.10.1 Gemcitabine dosing: Adjustment for Toxicity

Non-hematologic toxicity (all indications):

- Hold or decrease gemcitabine dose by 50% for the following: Severe (Grade 3 or 4) non-hematologic toxicity until resolved (excludes nausea, vomiting, or alopecia [no dose modifications recommended])
- Permanently discontinue gemcitabine for any of the following: Unexplained dyspnea (or other evidence of severe pulmonary toxicity), severe hepatotoxicity, hemolytic uremic syndrome (HUS), capillary leak syndrome (CLS), posterior reversible encephalopathy syndrome (PRES)

Investigator's Choice Chemotherapy - Dose Reductions for Hematologic Toxicity

Dose adjustments are based on nadir blood counts (assessed as per local standards) since the preceding drug administration. Dose level adjustments for investigator's choice chemotherapy are relative to that of the preceding administration. After the first cycle, growth factors may be used to assist hematologic recovery. Use local standards of care in the use of these supportive measures. Additionally, prophylactic antibiotics may be used according to local standards of care. Please report any antibiotic or growth factor use on the eCRF.

Table 4.5.10.1-1: Dose Modifications for Non-hematologic Toxicity

Toxicity	Gemcitabine	Pemetrexed	Carboplatin	Paclitaxel/Docetaxel
Febrile Neutropenia Grade ≥ 3	Reduce one dose level	Reduce one dose level	Reduce one dose level	Reduce one dose level
Diarrhea Grade ≥ 3	Reduce one dose level	Reduce one dose level	No change	Reduce one dose level
Allergic reaction Grade ≥ 3[a]	Discontinue	Discontinue	Discontinue	Discontinue
Neuropathy Grade 2	No change	No change	No change	Reduce one dose level
Neuropathy Grade ≥ 3	Discontinue	Discontinue	Discontinue	Discontinue

Table 4.5.10.1-1: Dose Modifications for Non-hematologic Toxicity

Toxicity	Gemcitabine	Pemetrexed	Carboplatin	Paclitaxel/Docetaxel
Calculated creatinine clearance < 50 ml/min	No change	No change	No change	No change
Other Grade ≥ 3 toxicity, except for fatigue and transient arthralgia and myalgia	Adjust as medically indicated	Adjust as medically indicated	Adjust as medically indicated	Adjust as medically indicated

[a] Only the drug causing the hypersensitivity or acute infusion reaction (≥ 3 Grade 3) require(s) discontinuation. All other drugs may continue.

Growth factors are permissible to allow for hematological recovery. Please use local standards of care in the use of these supportive measures. Additionally, the use of prophylactic dose antibiotics is to be used according to local standards of care. Please note any antibiotic or growth factor use on the eCRF.

4.5.11 Group D: Erlotinib Treatment Discontinuation

Discontinue erlotinib for:

- Interstitial Lung Disease (ILD)
- Severe hepatic toxicity that does not improve significantly or resolve within 3 weeks
- Gastrointestinal perforation
- Severe bullous, blistering or exfoliating skin conditions
- Corneal perforation or severe ulceration
- Because TKI and nivolumab may both cause gastrointestinal (GI), hepatic, skin, pulmonary, renal, and ocular toxicity, it is recommended that TKI also be discontinued if any such toxicities meeting nivolumab dose discontinuation criteria (above) occur.
- In addition, erlotinib should be discontinued for:
  - Any AEs specified in the local product label for erlotinib.
  - Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued erlotinib dosing.
- Any erlotinib dosing interruption > 6 weeks with the following exceptions:
  - Dosing interruptions to allow for prolonged steroid tapers to manage drug-related pneumonitis or interstitial lung disease. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the BMS Study Director/Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted
  - For non-drug-related reasons may be allowed if approved by the BMS medical monitor. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the BMS Study Director/Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted

Note: In Group D if the investigator assesses the drug-related AE to be related to nivolumab only and not related to erlotinib, nivolumab-dosing alone may be discontinued while erlotinib-dosing

is delayed until the subject meets criteria to resume erlotinib treatment. The case must be discussed with the BMS Study Director/Medical Monitor, and the relationship to nivolumab should be well documented in the source documents.

Discontinuation of erlotinib alone with delay of nivolumab-dosing may be permitted if the investigator assesses an AE meeting discontinuation criteria to be related to erlotinib-only and not to nivolumab, and the case is discussed with and approved by the BMS Study Director/Medical Monitor. In such cases, nivolumab dosing may resume when the criteria for resuming treatment (specified in Section 4.5.3.2) are met. Relationship to erlotinib should be well documented in the source documents.

4.5.12 Erlotinib Dose Modifications

Dose modifications for erlotinib should follow the labeled recommendations for modification.

4.5.13 Resumption of Erlotinib

Treatment may resume when the drug-related AE(s) resolve(s) to Grade 1 or baseline value. If treatment must be delayed for 6 weeks, please contact the Study Director/Medical Monitor before resuming dosing.

If a subject fails to meet criteria for re-treatment, then re-treatment should be delayed and the subject should be re-evaluated weekly or more frequently as clinically indicated.

If dosing of both nivolumab and erlotinib have been delayed, it is acceptable to resume dosing of nivolumab and erlotinib independently of each other. Erlotinib may be resumed in the setting of an ongoing corticosteroid taper, even at doses equivalent to or higher than prednisone 10 mg/day, as long as the drug-related AE has otherwise resolved to Grade 1 or baseline.

Any subject who fails to recover from toxicity attributable to erlotinib to baseline or Grade ≤ 1 within 6 weeks from the last dose given should discontinue erlotinib.

For erlotinib specifically, when resuming, please follow the local label recommendations for dose reductions.

4.5.14 Group E: Crizotinib Treatment Discontinuation

- ALT or AST elevation greater than 3 ×ULN with total bilirubin elevation greater than 2 ×ULN in the absence of cholestasis or hemolysis.
- Recurrent Grade 3 or 4 ALT or AST elevation or recurrent Grade 4 hematologic toxicity on 250 mg once daily:
- Any Grade treatment-related ILD/pneumonitis
- Grade 4 QTc prolongation or QTc interval prolongation in combination with Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia, or recurrent Grade 3 QTc prolongation at 250 mg once daily.
- Life-threatening bradycardia in subjects who are not taking a concomitant medication also known to cause bradycardia or known to cause hypotension

All subjects who discontinue investigational product should comply with protocol specified end of treatment and follow-up procedures as outlined in the schedule of events. Subjects will continue

with the on-study visit schedule. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness). If study treatment is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate CRF page.

4.5.15 Crizotinib Dose Modifications

If dose reduction is necessary, reduce dose to 200 mg orally twice daily; if necessary, further reduce to 250 mg once daily. If unable to tolerate 250 mg once daily, permanently discontinue therapy.

- Hematologic toxicity (except lymphopenia, unless lymphopenia is associated with clinical events such as opportunistic infection):
  - Grade 3 toxicity (WBC 1000-2000/mm^3, ANC 500-1000/mm^3, platelets 25,000-50,000/mm^3), Grade 3 anemia: Withhold treatment until recovery to ≤ Grade 2, then resume at the same dose and schedule.
  - Grade 4 toxicity (WBC < 1000/mm^3, ANC < 500/mm^3, platelets < 25,000/mm^3), Grade 4 anemia: Withhold treatment until recovery to ≤ Grade 2, then resume at 200 mg twice daily.
  - Recurrent Grade 4 toxicity on 200 mg twice daily: Withhold treatment until recovery to ≤ Grade 2, then resume at 250 mg once daily.
  - Recurrent Grade 4 toxicity on 250 mg once daily: Permanently discontinue.
- Non-hematologic toxicities:
  - Cardiovascular toxicities:
    - QT_c prolongation:
      - Grade 3 QT_c prolongation (QT_c > 500 msec without life-threatening signs or symptoms) on at least 2 separate ECGs: Withhold treatment until recovery to baseline or to ≤ Grade 1 (QT_c ≤ 480 msec), then resume at 200 mg twice daily.
      - Recurrent Grade 3 QTc prolongation at 200 mg twice daily: Withhold treatment until recovery to baseline or to ≤ Grade 1, then resume at 250 mg once daily.
      - Recurrent Grade 3 QTc prolongation at 250 mg once daily: Permanently discontinue.
      - Grade 4 QTc prolongation (QTc > 500 msec or ≥ 60 msec change from baseline with life-threatening symptoms): Permanently discontinue.
    - Bradycardia:
      - Grade 2 bradycardia (symptomatic with medical intervention indicated) or Grade 3 bradycardia (severe/medically significant with intervention indicated): Withhold until recovery to asymptomatic bradycardia or to a heart rate of ≥ 60 beats/minute and evaluate concomitant medications. If contributing concomitant medication is identified and discontinued (or dose adjusted), then resume crizotinib at the previous dose. If no contributing concomitant medication is identified (or cannot be discontinued or dose-adjusted), resume crizotinib at a reduced dose.

- Grade 4 bradycardia due to crizotinib (life-threatening with urgent intervention indicated): Permanently discontinue.
- Grade 4 bradycardia associated with concurrent medications known to cause bradycardia or hypotension (life-threatening with urgent intervention indicated): Withhold until recovery to asymptomatic bradycardia or to a heart rate of ≥ 60 beats/minute, and if concurrent medication can be discontinued or dose adjusted, resume at 250 mg once daily with frequent monitoring.

♦ Hepatotoxicity: Hepatotoxicity **during** treatment:

- Grade 3 or 4 ALT or AST elevation (ALT or AST >5 ×ULN) with ≤ Grade 1 total bilirubin elevation (total bilirubin ≤1.5 ×ULN): Withhold treatment until recovery to ≤ Grade 1 (<3 ×ULN) or baseline, then resume at 200 mg twice daily.
- Recurrent Grade 3 or 4 ALT or AST elevation with ≤ Grade 1 total bilirubin elevation: Withhold treatment until recovery to ≤ Grade 1, then resume at 250 mg once daily.
- Recurrent Grade 3 or 4 ALT or AST elevation on 250 mg once daily: Permanently discontinue.
- Grade 2, 3, or 4 ALT or AST elevation (ALT or AST >3 ×ULN) with concurrent Grade 2, 3, or 4 total bilirubin elevation (> 1.5 ×ULN) in the absence of cholestasis or hemolysis: Permanently discontinue.
- Pulmonary toxicity: ILD/pneumonitis (any grade; not attributable to disease progression, infection, other pulmonary disease or radiation therapy): Permanently discontinue.

4.5.16 Treatment of Nivolumab-Related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the study medical monitor or designee and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (Version 4.0) guidelines. Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

- **For Grade 1 symptom: (Mild reaction; infusion interruption not indicated; intervention not indicated).**
  - Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional nivolumab administrations. Infusion time can be increased to 60 minute or longer if needed.
- **For Grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti-**

inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for ≤ 24 hours).

- Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further nivolumab will be administered at that visit.
- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before nivolumab infusions. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used. Infusion time can be increased to 60 minute or longer if needed.

- **For Grade 3 or 4 symptoms: (Severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]. Grade 4: Life-threatening; pressor or ventilatory support indicated).**
  - **Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline and treat the subject as follows:** Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the Investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms. In case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

4.5.17 Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD. Subjects treated with nivolumab or nivolumab-containing regimens will be permitted to continue treatment beyond initial RECIST v1.1 defined PD as long as the following criteria are met:

1) Investigator-assessed clinical benefit and do not have rapid disease progression
2) Tolerance of study drug
3) Stable performance status

4) Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
5) The decision to continue treatment beyond initial progression has been discussed with the BMS Medical Monitor or designee and is documented in the study records. The written informed consent signed by the subject at study entry prior to receiving nivolumab (ie, prior to PD) will serve as documentation that the subject understands any foreseeable risks or discomforts, or other alternative treatment options if the subject decides to continue nivolumab treatment post-progression. No separate post-progression informed consent form is required.

A radiographic assessment/ scan is performed within 8 weeks of original PD to determine whether there has been a decrease in the tumor size, or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment with nivolumab.

If the investigator feels that the nivolumab subject continues to achieve clinical benefit by continuing treatment, the subject should remain on the trial and continue to receive monitoring. For the subjects who continue nivolumab study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden according to RECIST v1.1 from time of initial PD. This includes an increase in the sum of all target lesions and/ or the development of new measurable lesions. Treatment should be discontinued permanently upon documentation of further disease progression. New lesions are considered measureable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). Any new lesion considered non-measureable at the time of initial progression may become measureable and therefore included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm).

Subjects with global deterioration of health status who require discontinuation of treatment without objective evidence of disease progression at the time of treatment discontinuation should be reported as ‘symptomatic deterioration’. Every effort should be made to document objective progression (ie, radiographic confirmation) even after discontinuation of treatment.

4.7 Management for Erlotinib related adverse events

No specific algorithm exists to manage toxicities related to erlotinib. Recommendations provided in local label recommendations should be followed by the investigator. Additionally, a recently published review article on the management of common toxicities in metastatic NSCLC related to anti-lung cancer therapies with EGFR–TKIs[92] can be consulted and is included in Appendix 1.

4.8 Management of standard of care agents (chemotherapy or bevacizumab) related adverse events

No specific algorithm exists to manage toxicities related to SOC agents. Recommendations provided in local label recommendations should be followed by the investigator.

4.9 Blinding/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.

4.10 Treatment Compliance

Treatment compliance will be monitored by drug accountability as well as the subject's medical record and eCRF.

4.11 Destruction of Study Drug

For this study, study drugs (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials and syringes may be destroyed on site.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.

- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met, the responsible Study Monitor will arrange for return of study drug.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

4.12 Return of Study Drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible Study Monitor.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Assessments and Procedures (28 days) - All Subjects

*** Note: as per Amendments 03 and 04, Groups A, B, C, and D have closed enrollment and Group E was permanently terminated.**

Procedure	Screening	Notes
ELIGIBILITY ASSESSMENTS		
Informed Consent	X	
Inclusion/Exclusion Criteria	X	Assessed prior to randomization
Medical History	X	
SAFETY ASSESSMENTS		
Physical Measurements (including weight and height)	X	Within 28 days prior to first dose
Physical Examination	X	Within 28 days prior to first dose
ECOG Performance Status	X	Within 28 days prior to first dose
Vital Signs and Oxygen Saturation	X	Temperature, BP, HR, RR, O_2 saturation by pulse oximetry (also monitor amount of supplemental oxygen if applicable) Obtain vital signs at screening visit and within 72 hours of first dose. For oxygen saturation, please see Section 5.3 for details.
SAE Assessment	X	Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures.
Assessment of Signs and Symptoms	X	After obtaining Informed Consent, assess all signs and symptoms within 14 days of study randomization, prior to study treatment initiation.
[redacted]		
Pregnancy Testing (WOCBP Only)	X	Serum or urine pregnancy test to be performed locally **within 24 hours** prior to first dose

Table 5.1-1: Screening Assessments and Procedures (28 days) - All Subjects		
*** Note: as per Amendments 03 and 04, Groups A, B, C, and D have closed enrollment and Group E was permanently terminated.**		
Procedure	**Screening**	**Notes**
Hematology Test, Chemistry Test, and Liver Function Test	X	Labs performed locally within 14 days prior to first dose: Hematology Test includes WBC count with 3-part differential, ANC, lymphocyte count, hemoglobin, hematocrit, and platelet count. Chemistry Test include BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, and bicarbonate, glucose, LDH. Liver Function Test includes aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase and albumin.
Thyroid Function Testing	X	Includes TSH, free T3 and free T4. Performed locally within 14 days prior to first dose.
Hepatitis B & C Testing (HBV sAg and HCV Ab or HCV RNA)	X	Includes HBV sAg and HCV Ab or HCV RNA. Performed locally within 28 days prior to first dose.
ECG (12-lead)	X	ECG will be performed and assessed locally.
EFFICACY ASSESSMENTS		
Radiographic Tumor Assessment (chest, abdomen, pelvis, brain)	X	Performed **within 21 days prior to first dose**. CT of chest, abdomen, pelvis, and additional sites of known or suspected disease. MRI of brain or CT with contrast for subjects with known brain metastasis or if clinically indicated. See Section 5.4 for details. Subjects with evidence of disease progression after completion of induction therapy (Groups A and B) are not eligible to enroll.
Assignment and Distribution of ActiGraph Monitoring Device to Group C patients	X	All subjects eligible for Group C will be provided with an ActiGraph device at screening to be used continuously for at least 7 days prior to the first dose. Subjects who become screen failures will return their device.
[redacted]		

Table 5.1-1: Screening Assessments and Procedures (28 days) - All Subjects		
* Note: as per Amendments 03 and 04, Groups A, B, C, and D have closed enrollment and Group E was permanently terminated.		
Procedure	**Screening**	**Notes**
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
IWRS / CLINICAL DRUG SUPPLIES		
IWRS	X	For subject number assignment at the time informed consent is obtained.

ALK=anaplastic lymphoma kinase; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EGFR=epidermal growth factor receptor; FPFPE=formalin-fixed paraffin-embedded; IWRS=interactive web response service; NSQ=non-squamous.

Table 5.1-2: Group A- On-Study Assessments - Treatment Phase				
Note: Subjects start Cycle 1 once randomized to a maintenance therapy arm. Investigator's choice chemotherapy is not on-study.				
Procedure	**Cycle 1 Day 1**	**Each Subsequent Cycle Day 1 (Cycle 2 onwards)**	**End of Treatment[a]**	**Notes**
SAFETY ASSESSMENTS				
Physical Measurements (including weight)	X	X	X	
Targeted physical examination	X	X	X	
ECOG Performance Status	X	X	X	ECOG within 72 hours prior to each dose
Vital Signs and Oxygen Saturation	X	X	X	Within 72 hours prior to dosing and at EOT. Include temperature, blood pressure, heart rate, respiratory rate. For oxygen saturation, please see Section 5.3 for details.
Adverse Events Assessment	Continuously during study			Monitoring for AEs in pemetrexed or bevacizumab receiving subjects should follow recommendations specified in the respective package inserts.
[redacted]	[redacted]	[redacted]	[redacted]	
Hematology Tests		X	X	Includes WBC count with 3-part differential, ANC, lymphocyte count, hemoglobin, hematocrit, and platelet count
Chemistry Tests		X	X	Chemistry (BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, and bicarbonate, glucose), LDH
Liver Function Test		X	X	Includes aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, albumin

Table 5.1-2: Group A- On-Study Assessments - Treatment Phase				
Note: Subjects start Cycle 1 once randomized to a maintenance therapy arm. Investigator's choice chemotherapy is not on-study.				
Procedure	**Cycle 1 Day 1**	**Each Subsequent Cycle Day 1 (Cycle 2 onwards)**	**End of Treatment[a]**	**Notes**
Thyroid Function Testing			X	TSH should be evaluated every 6 weeks and EOT. However, reflexive free T3 and free T4 should be performed if TSH is abnormal.
Pregnancy Testing (WOCBP Only)	X	• Every 3 weeks • Every 4 weeks for nivolumab monotherapy arms	X	Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to first dose, and then a negative test every 3 weeks (every 4 week for the nivolumab monotherapy arms).
EFFICACY ASSESSMENTS				
Radiographic Tumor Assessment (chest, abdomen, and known sites of disease)	Beginning at week 9 (± 1 week), then every 8 weeks (± 1 week) for up to 2 years.			CT/MRI of brain (with contrast, unless contraindicated) required every 12 weeks for subjects who have known history of brain metastases or if clinically indicated.
[redacted]				
OUTCOMES RESEARCH ASSESSMENTS				

Table 5.1-2: Group A- On-Study Assessments - Treatment Phase				
Note: Subjects start Cycle 1 once randomized to a maintenance therapy arm. Investigator's choice chemotherapy is not on-study.				
Procedure	**Cycle 1 Day 1**	**Each Subsequent Cycle Day 1 (Cycle 2 onwards)**	**End of Treatment[a]**	**Notes**
Patient Outcomes Assessment (PRO) (FACT-L and EQ-5D)	X	• From 0-3 months: every 2 weeks for nivolumab-monotherapy subjects and; every 3 weeks for all other arms. • Between Months 4 and 12: every 6 weeks for both treatment arms • After 12 months: every 12 weeks for both arms.	X	Obtained at the site prior to any study procedures or dosing.
Health Care Resource Utilization		• Every 6 weeks for the first year • Every 12 weeks thereafter	X	First assessment at Week 6.
CLINICAL DRUG SUPPLIES AND STUDY DRUG ADMINISTRATION				
IWRS	X	X	X	Patients' screening, all drug assignment, and EOT visits will be collected in the IWRS system
IWRS Vial Assignment	X	X		• Within 1 week prior to first dose on study. • Note: The first dose on treatment must be within 42 days of last induction chemotherapy treatment.

Table 5.1-2: Group A- On-Study Assessments - Treatment Phase				
Note: Subjects start Cycle 1 once randomized to a maintenance therapy arm. Investigator's choice chemotherapy is not on-study.				
Procedure	**Cycle 1 Day 1**	**Each Subsequent Cycle Day 1 (Cycle 2 onwards)**	**End of Treatment[a]**	**Notes**
Nivolumab 240 mg every 2 weeks OR Nivolumab 5 mg/kg every 3 weeks with Bevacizumab or Pemetrexed	X	X		Nivolumab administration is ± 3 days but no less than 18 days from previous dose (no less than 12 days from previous dose in nivolumab monotherapy arms). Study drug infusion start and stop times (± 5mins) will be recorded. Nivolumab is to be administered first, bevacizumab or pemetrexed start at least 30 minutes after completion of the nivolumab infusion. Treatment to continue until progression, withdrawal of consent, unacceptable toxicity, a maximum of 24 months or study closure, whichever occurs first
Termination of study medication			X	

[a] If the decision to permanently discontinue the study treatments is taken during a scheduled visit, the End Of Treatment (EOT) visit should be performed instead of the scheduled visit (or within 7 calendar days after last drug administration)

AEs=adverse events; ECOG=Eastern Cooperative Oncology Group; EQ-5D=EuroQol Five Dimension; EOT=end of treatment; FACT-L=Functional Assessment of Cancer Therapy-Lung Cancer Subscale; IWRS=interactive web response system; PRO=patient-reported outcomes; WOCBP=women of child-bearing potential.

Table 5.1-3: Group A- Follow-Up Procedural Outline			
Procedure	**Follow-Up Visits 1 & 2[a]**	**Survival Visits[b]**	**Notes**
SAFETY ASSESSMENTS			
Targeted Physical Examination	X		To assess for potential late emergent study drug-related issues.
Vital Signs	X		
Adverse Event Assessment	X		At least 100 days from the last dose of therapy, subjects will be followed for ongoing drug-related AEs until resolved, return to baseline or deemed irreversible, or until lost to follow-up, withdrawal of study consent, or start of subsequent therapy.
[redacted]	[redacted]		
Chemistry Test	X		Required at Visit 1. Repeat at Visit 2 only if study drug-related toxicity persists.
Hematology Test	X		Required at Visit 1. Repeat at Visit 2 only if study drug-related toxicity persists.
[redacted]			
EFFICACY ASSESSMENTS			
Radiographic Tumor Assessment (chest, abdomen, and known sites of disease)	X	X	• Only for subjects not assessed to have progression by the radiology review prior to entering Post-treatment Phase. • Every 8 weeks (± 1 week) for up to 2 years.
OUTCOMES RESEARCH ASSESSMENTS			
Patient Outcomes Assessment (PRO): FACT-L, EQ-5D	X	EQ-5D only	• PRO to be collected at both Follow-up Visits 1 and 2. • In Survival Visits, EQ-5D is collected every 3 months (± 1 week) for the first year of the Follow-Up Phase, then every 6 months (± 2 weeks) thereafter. • PRO can be collected by mail/phone for long-term assessments occurring after Follow-up Visit 2.

Table 5.1-3: Group A- Follow-Up Procedural Outline

Procedure	Follow-Up Visits 1 & 2[a]	Survival Visits[b]	Notes
Health Care Resource Utilization	X		Assessments to be taken at the both follow up visits following discontinuation
Collection of Survival Status	X	X	• Collect every 3 months (±1 week) in Survival Visits until death, lost to follow-up, withdrawal of study consent, or for 4 years after the start of study treatment. • May be performed by phone contact or office visit • Will include collection of subsequent anti-cancer therapy information

[a] Follow-Up Visit 1 is to occur 35 days from the last dose of study treatment (±7 days). Follow-Up Visit 2 to occur 80 days from Follow-Up Visit 1 (± 7 days).

[b] Survival Follow-Up Visits to occur approximately every 3 months (± 1 week) from Follow-Up Visit 2.

AEs=adverse events; ECOG=Eastern Cooperative Oncology Group; EQ-5D=EuroQol Five Dimension; EOT=end of treatment; FACT-L=Functional Assessment of Cancer Therapy-Lung Cancer Subscale; IWRS=interactive web response system; PRO=patient-reported outcomes; WOCBP=women of child-bearing potential.

Table 5.1-4:	**Group B- On-Study Assessments - Treatment Phase (1 cycle =2 weeks, Arm A: nivolumab 240 mg every 2 weeks; Arm B: Best Supportive Care every 2 weeks)**			
Note: Subjects start Cycle 1 once randomized to a maintenance therapy arm. Investigator's Choice chemotherapy is not on-study.				
Procedure	**Cycle 1 Day 1**	**Each Subsequent Cycle Day 1 (Cycle 2 onwards)**	**End of Treatment[a]**	**Notes**
SAFETY ASSESSMENTS				
Physical Measurements (including weight)	X	X	X	
Targeted physical examination	X	X	X	
ECOG Performance Status	X	X	X	ECOG within 72 hours prior to each dose
Vital Signs and Oxygen Saturation	X	X	X	Within 72 hours prior to dosing and at EOT. Include temperature, blood pressure, heart rate, respiratory rate. For oxygen saturation, please see Section 5.3 for details.
Adverse Events Assessment	Continuously during study			
[redacted]				
Hematology Tests		X	X	Includes WBC count with 3-part differential, ANC, lymphocyte count, hemoglobin, hematocrit, and platelet count
Chemistry Tests		X	X	Chemistry (BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, and bicarbonate, glucose), LDH
Liver Function Test		X	X	Includes aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, albumin

Table 5.1-4: Group B- On-Study Assessments - Treatment Phase (1 cycle =2 weeks, Arm A: nivolumab 240 mg every 2 weeks; Arm B: Best Supportive Care every 2 weeks)

Note: Subjects start Cycle 1 once randomized to a maintenance therapy arm. Investigator's Choice chemotherapy is not on-study.

Procedure	Cycle 1 Day 1	Each Subsequent Cycle Day 1 (Cycle 2 onwards)	End of Treatment[a]	Notes
Thyroid Function Testing			X	TSH should be evaluated every 6 weeks and EOT. However, reflexive free T3 and free T4 should be performed if TSH is abnormal.
Pregnancy Testing (WOCBP Only)	X	Arm A	X	Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug, and at least every 4 weeks on study, and every cycle for Arm A.
EFFICACY ASSESSMENTS				
Radiographic Tumor Assessment (chest, abdomen, and known sites of disease)	Beginning Week 9 (±1 week), then every 8 weeks (±1 week) for up to 2 years.			CT/MRI of brain (with contrast, unless contraindicated) required every 12 weeks for subjects who have known history of brain metastases or if clinically indicated.
[redacted]				
OUTCOMES RESEARCH ASSESSMENTS				

Table 5.1-4:	**Group B- On-Study Assessments - Treatment Phase (1 cycle =2 weeks, Arm A: nivolumab 240 mg every 2 weeks; Arm B: Best Supportive Care every 2 weeks)**			
Note: Subjects start Cycle 1 once randomized to a maintenance therapy arm. Investigator's Choice chemotherapy is not on-study.				
Procedure	**Cycle 1 Day 1**	**Each Subsequent Cycle Day 1 (Cycle 2 onwards)**	**End of Treatment[a]**	**Notes**
Patient Outcomes Assessment (PRO) (FACT-L and EQ-5D)	X	• From 0-3 months: every 2 weeks • Between Months 4 and 12: Every 6 weeks • After 12 months:: every 12 weeks.	X	Obtained at the site prior to any study procedures or dosing.
CLINICAL DRUG SUPPLIES AND STUDY DRUG ADMINISTRATION				
IWRS	X	X	X	Patients screening, all drug assignment, and EOT visits will be collected in the IWRS system
IWRS Vial Assignment	X	X		Within 1 week prior to first dose on study. Note: The first dose on treatment must be within 42 days of last induction chemotherapy treatment.
Nivolumab 240 mg every 2 weeks	X	X		Nivolumab administration is ± 3 days but no less than 12 days from previous dose. Study drug infusion start and stop times (± 5mins) will be recorded. Treatment to continue until progression, withdrawal of consent, unacceptable toxicity, a maximum of 24 months or study closure, whichever occurs first.
Termination of study medication			X	

[a] If the decision to permanently discontinue the study treatments is taken during a scheduled visit, the End Of Treatment (EOT) visit should be performed instead of the scheduled visit (within 7 calendar days after last drug administration)

AEs=adverse events; ECOG=Eastern Cooperative Oncology Group; EQ-5D=EuroQol Five Dimension; EOT=end of treatment; FACT-L=Functional Assessment of Cancer Therapy-Lung Cancer Subscale; IWRS=interactive web response system; PRO=patient-reported outcomes; WOCBP=women of child-bearing potential.

Table 5.1-5: Group B- Follow-Up Procedural Outline

Procedure	Visits 1 & 2[a]	Survival Visits[b]	Notes
SAFETY ASSESSMENTS			
Targeted Physical Examination	X		To assess for potential late emergent study drug-related issues.
Vital Signs	X		
Adverse Event Assessment	X		At least 100 days from the last dose of therapy, subjects will be followed for ongoing drug-related AEs until resolved, return to baseline or deemed irreversible, or until lost to follow-up, withdrawal of study consent, or start of subsequent therapy.
[redacted]	[redacted]		
Chemistry Test	X		Required at Visit 1. Repeat at Visit 2 only if study drug-related toxicity persists.
Hematology Test	X		Required at Visit 1. Repeat at Visit 2 only if study drug-related toxicity persists.
[redacted]			
[redacted]			[redacted]
EFFICACY ASSESSMENTS			
Radiographic Tumor Assessment (chest, abdomen, and known sites of disease)	X	X	• Only for subjects not assessed to have progression by the radiology review prior to entering Post-treatment Phase. • Every 8 weeks (± 1 week) for up to 2 years.
OUTCOMES RESEARCH ASSESSMENTS			
Patient Outcomes Assessment (PRO): FACT-L and EQ-5D	X	EQ-5D only	• PRO to be collected at both Follow-up Visits 1 and 2. • In Survival Visits, EQ-5D is collected every 3 months (± 1 week) for the first year of the Follow-Up Phase, then every 6 months (± 2 weeks) thereafter. • PRO can be collected by mail/phone for long-term assessments occurring after Follow-up Visit 2.

Table 5.1-5: Group B- Follow-Up Procedural Outline

Procedure	Visits 1 & 2[a]	Survival Visits[b]	Notes
Collection of Survival Status	X	X	• Collect every 3 months (± 1 week) in Survival Visits until death, lost to follow-up, withdrawal of study consent, or for 4 years after the start of the study treatment • May be performed by phone contact or office visit. • Will include collection of subsequent anti-cancer therapy information

[a] For Arm A, Follow-Up Visit 1 is to occur 35 days from the last dose of study treatment (± 7 days). Follow-Up Visit 2 to occur 80 days from Follow-Up Visit 1 (± 7 days). For Arm B, Follow-up Visit 1 to occur 35 days from the last clinic visit date (±7 days).

[b] Survival Follow-Up Visits to occur approximately every 3 months (± 1 week) from Follow-Up Visit 2.

AEs=adverse events; EQ-5D=EuroQol Five Dimension; EOT=end of treatment; FACT-L=Functional Assessment of Cancer Therapy-Lung Cancer Subscale; IWRS=interactive web response system; PRO=patient-reported outcomes; WOCBP=women of child-bearing potential.

Table 5.1-6: Group C- On-Study Assessments - Treatment Phase Arm A (Investigator's Choice cycle = every 3 weeks[a]), Arm B (nivolumab cycle = 2 weeks, nivolumab 240 mg every 2 weeks)				
Procedure	**Cycle 1 Day 1**	**Each Subsequent Cycle Day 1 (Cycle 2 onwards)**	**End of Treatment[b]**	**Notes**
SAFETY ASSESSMENTS				
Physical Measurements (including weight)	X	X	X	
Targeted physical examination	X	X	X	
ECOG Performance Status	X	X	X	ECOG within 72 hours prior to each dose
Vital Signs and Oxygen Saturation	X	X	X	Within 72 hours prior to dosing and at EOT. Include temperature, blood pressure, heart rate, respiratory rate. For oxygen saturation, please see Section 5.3 for details.
Adverse Events Assessment	Continuously during study			Monitoring for adverse events related to chemotherapy drugs should follow recommendations specified in the local labels.
[redacted]	[redacted]	[redacted]	[redacted]	
Hematology Tests		X	X	Includes WBC count with 3-part differential, ANC, lymphocyte count, hemoglobin, hematocrit, and platelet count
Chemistry Tests		X	X	Chemistry (BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, and bicarbonate, glucose), LDH
Liver Function Test		X	X	Includes aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, albumin

Table 5.1-6:	**Group C- On-Study Assessments - Treatment Phase Arm A (Investigator's Choice cycle = every 3 weeks[a]), Arm B (nivolumab cycle = 2 weeks, nivolumab 240 mg every 2 weeks)**			
Procedure	**Cycle 1 Day 1**	**Each Subsequent Cycle Day 1 (Cycle 2 onwards)**	**End of Treatment[b]**	**Notes**
Thyroid Function Testing			X	TSH should be evaluated every 6 weeks and EOT. However, reflexive free T3 and free T4 should be performed if TSH is abnormal.
Pregnancy Testing (WOCBP Only)	X		X	Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug, and at least every 4 weeks on study.
EFFICACY ASSESSMENTS				
Radiographic Tumor Assessment (chest, abdomen, and known sites of disease)	Beginning Week 9 (±1 week) then every 8 weeks (± 1 week) for up to 2 years.			CT/MRI of brain (with contrast, unless contraindicated) required every 12 wks for subjects who have known history of brain metastases or if clinically indicated.
[redacted]				
[redacted]	[redacted]		[redacted]	[redacted]
[redacted]	[redacted]			
OUTCOMES RESEARCH ASSESSMENTS				

Table 5.1-6:	**Group C- On-Study Assessments - Treatment Phase Arm A (Investigator's Choice cycle = every 3 weeks[a]), Arm B (nivolumab cycle = 2 weeks, nivolumab 240 mg every 2 weeks)**			
Procedure	**Cycle 1 Day 1**	**Each Subsequent Cycle Day 1 (Cycle 2 onwards)**	**End of Treatment[b]**	**Notes**
Patient Outcomes Assessment (PRO) : FACT-L and EQ-5D	X	• From 0 to 3 months: every 2 weeks for nivolumab-monotherapy subjects and; those receiving IC every 2 weeks; every 3 weeks for subjects receiving IC therapy every 1 or 3 weeks. • Between Months 4 and 12: Every 6 weeks for all treatment arms • After 12 months: every 12 weeks for all treatment arms.	X	Obtained at the site prior to any study procedures or dosing.

Table 5.1-6:	**Group C- On-Study Assessments - Treatment Phase Arm A (Investigator's Choice cycle = every 3 weeks[a]), Arm B (nivolumab cycle = 2 weeks, nivolumab 240 mg every 2 weeks)**			
Procedure	**Cycle 1 Day 1**	**Each Subsequent Cycle Day 1 (Cycle 2 onwards)**	**End of Treatment[b]**	**Notes**
ActiGraph	• Continuous 24 hour monitoring will begin from screening at least 1 week prior to initiation of therapy, and continue to 6 months of treatment		At end of treatment or discontinuation, subjects will undergo 24 hour monitoring for 7 days.	• ActiGraph device will be removed for MRIs or charging. • The ActiGraph device will be provided at enrollment
Health Care Resource Utilization		• Every 6 weeks for the first year • Every 12 weeks thereafter	X	First assessment at Week 6.
CLINICAL DRUG SUPPLIES AND STUDY DRUG ADMINISTRATION				
IWRS	X	X	X	Patients' screening, all drug assignment, and EOT visits will be collected in the IWRS system
IWRS Vial Assignment	X	X		Within 1 week prior to dosing.
Nivolumab 240 mg every 2 weeks OR Investigator's Choice Chemotherapy	X	X		Nivolumab administration is ± 3 days but no less than 12 days from previous dose. Study drug infusion start and stop times (± 5mins) will be recorded. Nivolumab will continue until progression, withdrawal of consent, unacceptable toxicity, a maximum of 24 months or study closure, whichever occurs first
Termination of study medication			X	

[a] Investigators have option of following up subject every 1-3 weeks on chemo therapy, using local institutional standard for supportive management including growth factor support.

[b] If the decision to permanently discontinue the study treatments is taken during a scheduled visit, the End Of Treatment (EOT) visit should be performed instead of the scheduled visit (within 7 calendar days after last drug administration)

ECOG=Eastern Cooperative Oncology Group; EQ-5D=EuroQol Five Dimension; EOT=end of treatment; FACT-L=Functional Assessment of Cancer Therapy-Lung Cancer Subscale; IC=Investigator's Choice; IWRS=interactive web response system; PRO=patient-reported outcomes; WOCBP=women of child-bearing potential.

Table 5.1-7: Group C- Follow-Up Procedural Outline			
Procedure	**Visits 1 & 2[a]**	**Survival Visits[b]**	**Notes**
SAFETY ASSESSMENTS			
Targeted Physical Examination	X		To assess for potential late emergent study drug-related issues.
Vital Signs	X		
Adverse Event Assessment	X		At least 100 days from the last dose of therapy, subjects will be followed for ongoing drug-related AEs until resolved, return to baseline or deemed irreversible, or until lost to follow-up, withdrawal of study consent, or start of subsequent therapy.
[redacted]	[redacted]		
Chemistry Test	X		Required at Visit 1. Repeat at Visit 2 only if study drug-related toxicity persists.
Hematology Test	X		Required at Visit 1. Repeat at Visit 2 only if study drug-related toxicity persists.
[redacted]			
[redacted]			[redacted]
EFFICACY ASSESSMENTS			
Radiographic Tumor Assessment (chest, abdomen, and known sites of disease)	X	X	• Only for subjects not assessed to have progression by the radiology review prior to entering Post-treatment Phase. • Every 8 weeks (± 1 week) for up to 2 years.
OUTCOMES RESEARCH ASSESSMENT			
Patient Outcomes Assessment (PRO): FACT-L and EQ-5D	X	EQ-5D only	• PRO to be collected at both Follow-up Visits 1 and 2. • In Survival Visits, EQ-5D is collected every 3 months (± 1 week) for the first year of the Follow-Up Phase, then every 6 months (± 2 weeks) thereafter. • PRO can be collected by mail/phone for long-term assessments occurring after Follow-up Visit 2.

Table 5.1-7: Group C- Follow-Up Procedural Outline			
Procedure	**Visits 1 & 2[a]**	**Survival Visits[b]**	**Notes**
ActiGraph	X		At Follow-up Visit 1, subjects will undergo 7 days of continuous 24-hour monitoring. The device will be removed for MRIs, and charging.
Return of ActiGraph Device		X	The ActiGraph device will be returned at Follow-up Visit2.
Health Care Resource Utilization	X		Assessments to be taken at the both follow up visits following discontinuation
Collection of Survival Status	X	X	• Collect every 3 months (± 1 week) in Survival Visits until death, lost to follow-up, withdrawal of study consent, or for 4 years after the start of study treatment. May be performed by phone contact or office visit. • Will include collection of subsequent anti-cancer therapy information

[a] Follow-Up Visit 1 is to occur 35 days from the last dose of study treatment (±7 days). Follow-Up Visit 2 to occur 80 days from Follow-Up Visit 1 (± 7 days).

[b] Survival Follow-Up Visits to occur approximately every 3 months (± 1 week) from Follow-Up Visit 2.

ECOG=Eastern Cooperative Oncology Group; EQ-5D=EuroQol Five Dimension; FACT-L=Functional Assessment of Cancer Therapy-Lung Cancer Subscale; IWRS=interactive web response system; PRO=patient-reported outcomes; WOCBP=women of child-bearing potential.

Table 5.1-8: Group D: On-Study Assessments - Treatment Phase (1 cycle = 2 weeks, Arm A: erlotinib; Arm B: nivolumab 240 mg every 2 weeks)				
Procedure	**Cycle 1 Day 1**	**Each Subsequent Cycle Day 1 (Cycle 2 onwards)**	**End of Treatment[a]**	**Notes**
SAFETY ASSESSMENTS				
Physical Measurements (including weight)	X	X	X	
Targeted physical examination	X	X	X	
ECOG Performance Status	X	X	X	ECOG within 72 hours prior to each dose
Vital Signs and Oxygen Saturation	X	X	X	Within 72 hours prior to dosing and at EOT. Include temperature, blood pressure, heart rate, respiratory rate. For oxygen saturation, please see Section 5.3 for details.
Adverse Events Assessment	Continuously during study			Monitoring for AEs related to erlotinib should follow recommendations specified in the local labels.
[redacted]	[redacted]	[redacted]	[redacted]	
Hematology Tests		X	X	Includes WBC count with 3-part differential, ANC, lymphocyte count, hemoglobin, hematocrit, and platelet count. Except for Cycle 1 Day 1, the local lab tests should be repeated within 3 days prior to each dose.
Chemistry Tests		X	X	Chemistry (BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, and bicarbonate, glucose), LDH. Except for Cycle 1 Day 1, the local lab tests should be repeated within 3 days prior to each dose.
Liver Function Test		X	X	Includes aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase and albumin. Except for Cycle 1 Day 1, the local lab tests should be repeated within 3 days prior to each dose.

Table 5.1-8:	**Group D: On-Study Assessments - Treatment Phase (1 cycle = 2 weeks, Arm A: erlotinib; Arm B: nivolumab 240 mg every 2 weeks)**			
Procedure	**Cycle 1 Day 1**	**Each Subsequent Cycle Day 1 (Cycle 2 onwards)**	**End of Treatment[a]**	**Notes**
Thyroid Function Testing			X	TSH should be evaluated every 6 weeks and EOT. However, reflexive free T3 and free T4 should be performed if TSH is abnormal.
Pregnancy Testing (WOCBP Only)	X		X	Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug, and at least every 4 weeks on study.
EFFICACY ASSESSMENTS				
Radiographic Tumor Assessment (chest, abdomen, and known sites of disease)	Beginning Week 9 (±1 week), then every 8 weeks (± 1 week) for up to 2 years.			• CT/MRI of brain (with contrast, unless contraindicated) required every 12 weeks for subjects who have known history of brain metastases or if clinically indicated.
[redacted]				
[redacted]				
[redacted]	[redacted]		[redacted]	[redacted]
[redacted]	[redacted]			
[redacted]	[redacted]		[redacted]	[redacted]
OUTCOMES RESEARCH ASSESSMENTS				

Table 5.1-8:	**Group D: On-Study Assessments - Treatment Phase (1 cycle = 2 weeks, Arm A: erlotinib; Arm B: nivolumab 240 mg every 2 weeks)**			
Procedure	**Cycle 1 Day 1**	**Each Subsequent Cycle Day 1 (Cycle 2 onwards)**	**End of Treatment[a]**	**Notes**
Patient Outcomes Assessment (PRO): FACT-L and EQ-5D	X	• From 0-3 months: every 2 weeks • Between Months 4 and 12: Every 6 weeks • After 12 months:: every 12 weeks	X	Obtained at the site prior to any study procedures or dosing.
Health Care Resource Utilization		• Every 6 weeks for the first year • Every 12 weeks thereafter	X	First assessment at Week 6.
CLINICAL DRUG SUPPLIES AND STUDY ADMINISTRATION				
IWRS	X	X	X	Patients' screening, all drug assignment, and EOT visits will be collected in the IWRS system
IWRS Vial Assignment	X	X		Within 1 week prior to dosing.
Nivolumab 240 mg every 2 weeks OR Erlotinib 150 mg QD	X	X		Erlotinib dosing is daily throughout each cycle. Nivolumab administration is ±3 days but no less than 12 days from previous dose. Study drug infusion start and stop times (± 5mins) will be recorded. Nivolumab will continue until progression, withdrawal of consent, unacceptable toxicity, a maximum of 24 months, or study closure, whichever occurs first.
Termination of study medication			X	

[a] If the decision to permanently discontinue the study treatments is taken during a scheduled visit, the End Of Treatment (EOT) visit should be performed instead of the scheduled visit (within 7 calendar days after last drug administration).

ECOG=Eastern Cooperative Oncology Group; EQ-5D=EuroQol Five Dimension; FACT-L=Functional Assessment of Cancer Therapy-Lung Cancer Subscale; IWRS=interactive web response system; PRO=patient-reported outcomes; WOCBP=women of child-bearing potential.

Table 5.1-9: Group D- Follow-Up Procedural Outline			
Procedure	**Visits 1 & 2[a]**	**Survival Visits[b]**	**Notes**
SAFETY ASSESSMENTS			
Targeted Physical Examination	X		To assess for potential late emergent study drug-related issues.
Vital Signs	X		
Adverse Event Assessment	X		At least 100 days from the last dose of therapy, subjects will be followed for ongoing drug-related AEs until resolved, return to baseline or deemed irreversible, or until lost to follow-up, withdrawal of study consent, or start of subsequent therapy.
[redacted]	[redacted]		
Chemistry Test	X		Required at Visit 1. Repeat at Visit 2 only if study drug-related toxicity persists.
Hematology Test	X		Required at Visit 1. Repeat at Visit 2 only if study drug-related toxicity persists.
[redacted]			
[redacted]			[redacted]
[redacted]			
[redacted]			[redacted]
EFFICACY ASSESSMENTS			
Radiographic Tumor Assessment (chest, abdomen, and known sites of disease)	X	X	• Only for subjects not assessed to have progression by the radiology review prior to entering Post-treatment Phase. • Every 8 weeks (± 1 week) for up to 2 years.
OUTCOMES RESEARCH ASSESSMENTS			
Patient Outcomes Assessment (PRO): FACT-L and EQ-5D	X	EQ-5D only	• PRO to be collected at both Follow up Visits 1 and 2.

Table 5.1-9: Group D- Follow-Up Procedural Outline			
Procedure	**Visits 1 & 2[a]**	**Survival Visits[b]**	**Notes**
			• In Survival Visits, EQ-5D is collected every 3 months (± 1 week) for the first year of the Follow-Up Phase, then every 6 months (± 2 weeks) thereafter. • PRO can be collected by mail for long-term assessments occurring after Follow-up Visit 2.
Health Care Resource Utilization	X		Assessments to be taken at the both follow up visits following discontinuation
Collection of Survival Status	X	X	• Collect every 3 months (± 1 week) in Survival Visits until death, lost to follow-up, withdrawal of study consent, or for 4 years after the start of study treatment. • May be performed by phone contact or office visit. • Will include collection of subsequent anti-cancer therapy information

[a] Follow-Up Visit 1 is to occur 35 days from the last dose of study treatment (± 7 days). Follow-Up Visit 2 to occur 80 days from Follow-Up Visit 1 (± 7 days).

[b] Survival Follow-Up Visits to occur approximately every 3 months (± 1 week) from Follow-Up Visit 2.

ECOG=Eastern Cooperative Oncology Group; EQ-5D=EuroQol Five Dimension; FACT-L=Functional Assessment of Cancer Therapy-Lung Cancer Subscale; IWRS=interactive web response system; PRO=patient-reported outcomes; WOCBP=women of child-bearing potential.

Table 5.1-10: Group E- On-Study Assessments - Treatment Phase (1 cycle =2 weeks, nivolumab 240 mg every 2 weeks)				
***NOTE: Prior to Amendment 03, all subjects in Group E have entered the Follow-up phase. No additional combination treatment is to be given.**				
Procedure	**Cycle 1 Day 1**	**Each Subsequent Cycle Day 1: (Cycle 2 onwards)**	**End of Treatment**	**Notes**
SAFETY ASSESSMENTS				
Physical Measurements (including weight)	X	X	X	
Targeted physical examination	X	X	X	
ECOG Performance Status	X	X	X	ECOG within 72 hours prior to each dose
Vital Signs and Oxygen Saturation	X	X	X	Within 72 hours prior to dosing and at EOT. Include temperature, blood pressure, heart rate, respiratory rate. For oxygen saturation, please see Section 5.3 for details.
Adverse Events Assessment	Continuously during study			Monitoring for adverse events related to Crizotinib should follow recommendations specified in the local labels.
[redacted]	[redacted]	[redacted]	[redacted]	
Hematology Tests		X	X	Includes WBC count with 3-part differential, ANC, lymphocyte count, hemoglobin, hematocrit, and platelet count
Chemistry Tests		X	X	Chemistry (BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, and bicarbonate, glucose), LDH
Liver Function Test		X	X	Includes aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, albumin
Thyroid Function Testing			X	TSH should be evaluated every 6 weeks and EOT. However, reflexive free T3 and free T4 should be performed if TSH is abnormal.

Table 5.1-10:	**Group E- On-Study Assessments - Treatment Phase (1 cycle =2 weeks, nivolumab 240 mg every 2 weeks)**			
***NOTE: Prior to Amendment 03, all subjects in Group E have entered the Follow-up phase. No additional combination treatment is to be given.**				
Procedure	**Cycle 1 Day 1**	**Each Subsequent Cycle Day 1: (Cycle 2 onwards)**	**End of Treatment**	**Notes**
ECG (12-lead)	X		X	Evaluated every 8 weeks until 1 year, then every 12 weeks thereafter, and EOT
Pregnancy Testing (WOCBP Only)	X		X	Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug, and at least every 4 weeks on study.
EFFICACY ASSESSMENTS				
Radiographic Tumor Assessment (chest, abdomen, and known sites of disease)	Beginning Week 9 (±1 week), then every 8 weeks (± 1 week) for up to 2 years.			CT/MRI of brain (with contrast, unless contraindicated) required every 12 weeks for subjects who have known history of brain metastases or if clinically indicated.
[redacted]				
[redacted]	[redacted]		[redacted]	[redacted]
[redacted]	[redacted]			
OUTCOMES RESEARCH ASSESSMENTS				

Table 5.1-10: Group E- On-Study Assessments - Treatment Phase (1 cycle =2 weeks, nivolumab 240 mg every 2 weeks)				
***NOTE: Prior to Amendment 03, all subjects in Group E have entered the Follow-up phase. No additional combination treatment is to be given.**				
Procedure	**Cycle 1 Day 1**	**Each Subsequent Cycle Day 1: (Cycle 2 onwards)**	**End of Treatment**	**Notes**
Patient Outcomes Assessment (PRO): FACT-L and EQ-5D	X	• From 0-3 months: every 2 weeks • Between Months 4 and 12: every 6 weeks • After 12 months:: every 12 weeks	X	Obtained at the study site prior to any study procedures or dosing.
CLINICAL DRUG SUPPLIES AND STUDY DRUG ADMINISTRATION				
IWRS	X	X	X	Patients' screening, all drug assignment, and EOT visits will be collected in the IWRS system
IWRS Vial Assignment	X	X		Within 1 week prior to first dose on study
Nivolumab 240 mg every 2 weeks OR Crizotinib 250 mg BID	X	X		Crizotinib is given BID throughout cycle. Drug administration is ± 3 days but no less than 12 days from previous dose. Study drug infusion start and stop times (± 5 mins) will be recorded. Nivolumab is administered every 2 weeks over 30 minute infusion. Prior to Amendment 03, no additional combination treatment will be administered in Group E. All subjects previously enrolled in this Group will be monitored per the Follow up assessment schedule.
Termination of study medication			X	

BID=twice a day; ECOG=Eastern Cooperative Oncology Group; EQ-5D=EuroQol Five Dimension; FACT-L=Functional Assessment of Cancer Therapy-Lung Cancer Subscale; IWRS=interactive web response system; PRO=patient-reported outcomes; WOCBP=women of child-bearing potential.

Table 5.1-11: Group E-Follow-Up Procedural Outline			
Procedure	**Visits 1 & 2[a]**	**Survival Visits[b]**	**Notes**
SAFETY ASSESSMENTS			
Targeted Physical Examination	X		To assess for potential late emergent study drug-related issues.
Vital Signs	X		
Adverse Event Assessment	X		At least 100 days from the last dose of therapy, subjects will be followed for ongoing drug-related AEs until resolved, return to baseline or deemed irreversible, or until lost to follow-up, withdrawal of study consent, or start of subsequent therapy.
[redacted]	[redacted]		
Chemistry Test	X		Required at Visit 1. Repeat at Visit 2 only if study drug-related toxicity persists.
Hematology Test	X		Required at Visit 1. Repeat at Visit 2 only if study drug-related toxicity persists.
Liver Function Testing	X	X	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
ECG (12-lead)	X		Evaluated at Visit 1. Repeat at Visit 2 only if clinically indicated
[redacted]			
[redacted]			[redacted]

Table 5.1-11: Group E-Follow-Up Procedural Outline			
Procedure	**Visits 1 & 2[a]**	**Survival Visits[b]**	**Notes**
EFFICACY ASSESSMENTS			
Radiographic Tumor Assessment (chest, abdomen, and known sites of disease)	X	X	• Only for subjects not assessed to have progression by the radiology review prior to entering Post-treatment Phase. • Every 8 weeks (± 1 week) for up to 2 years.
OUTCOMES RESEARCH ASSESSMENTS			
Patient Outcomes Assessment (PRO): FACT-L and EQ-5D	X	EQ-5D only	• PRO to be collected at both Follow-up Visits 1 and 2. • In Survival Visits, EQ-5D is collected every 3 months (± 1 week) for the first year of the Follow-Up Phase, then every 6 months (± 2 weeks) thereafter. • PRO can be collected by mail/phone for long-term assessments occurring after Follow-up Visit 2.
Collection of Survival Status and Subsequent Therapy Information	X	X	• Collect every 3 months (± 1 week) in Survival Visits until death, lost to follow-up, withdrawal of study consent, or for 4 years after the start of study treatment. • May be performed by phone contact or office visit. • Will include collection of subsequent anti-cancer therapy information

[a] Follow-Up Visit 1 is to occur 35 days from the last dose of study treatment (± 7 days). Follow-Up Visit 2 to occur 80 days from Follow-Up Visit 1 (± 7 days).

[b] Survival Follow-Up Visits to occur approximately every 3 months (± 1 week) from Follow-Up Visit 2.

AEs=adverse events; ECOG=Eastern Cooperative Oncology Group; EQ-5D=EuroQol Five Dimension; FACT-L=Functional Assessment of Cancer Therapy-Lung Cancer Subscale; IWRS=interactive web response system; PRO=patient-reported outcomes; WOCBP=women of child-bearing potential.

5.1.1 Retesting During Screening Period

Retesting of laboratory parameters and/or other assessments during the Screening Period will be permitted (in addition to any parameters that require a confirmatory result).

Any new result will override the previous result (ie, the most current result prior to dosing) and is the value by which study inclusion will be assessed, as it represents the subject's most current, clinical state.

5.2 Study Materials

- NCI CTCAE version 4.0
- Nivolumab Investigator Brochure
- Laboratory manuals for collection and handling of blood and tissue specimens
- FACT-L, EQ-5D questionnaires
- Site manual for operation of interactive web response system
- Pharmacy Manual
- Serious Adverse Events (or eSAE) case report form pages
- Pregnancy Surveillance Forms
- RECIST v1.1 pocket guide
- BMS will provide ActiGraph accelerometers for measurement of Group C subject activity levels.
- Subject Brochure Card
- Patient Alert Card
- Electronic Case Report Form (eCRF) Completion Guidelines
- Reference Ring
- Safety Monitoring Call Guide

5.3 Safety Assessments

At baseline, a medical history will be obtained to capture relevant underlying conditions. The baseline examinations should include weight, height, ECOG Performance Status, blood pressure (BP), heart rate (HR), respiratory rate (RR), temperature, and oxygen saturation by pulse oximetry at rest and on exertion (also monitor amount of supplemental oxygen if applicable) should be performed within 28 days prior to first dose. Baseline signs and symptoms are those that are assessed within 14 days prior to first dose.

Concomitant medications will be collected from 14 days prior to the first dose through the study treatment period (see Table 5.1-1 and within the assessment tables for each sub-protocol).

Physical measurements including height, and weight (and calculated BSA for subjects receiving chemotherapy if needed) at screening. During treatment period and EOT, only body weight will be measured.

Baseline local laboratory assessments should be done within 14 days prior to first dose and are to include: WBC count with 3-part differential, ANC, lymphocyte count, hemoglobin, hematocrit, and platelet count, chemistry (BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, and bicarbonate, glucose, and LDH), liver function test (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin, alkaline phosphatase, albumin), and thyroid function test (TSH, free T3, and free T4).

The following baseline local laboratory assessments should be done within 28 days prior to first dose: Hepatitis B and C testing (HBV sAg and HCV Ab or HCV RNA).

Pregnancy testing for WOCBP (done locally) must be performed within 24 hours prior to the initial administration of study drug at baseline and then every 4 weeks (2 cycles) for subjects receiving nivolumab and every 3 weeks (each cycle) for subjects receiving chemotherapy. Pregnancy testing should also be performed at EOT for all subjects.

Subjects will be evaluated for safety if they have received any study drug. Toxicity assessments will be continuous during the treatment phase. During the Post-Chemotherapy and Nivolumab Follow-Up Phase at Visits 1 and 2, toxicity assessments should be done in person. Once subjects reach the survival follow-up phase, either in-person visits or documented telephone calls/email correspondence to assess the subject's status are acceptable.

Adverse events and laboratory values will be graded according to the NCI-CTCAE version 4.0. On-study weight, ECOG performance status, and vital signs should be assessed within 72 hours prior to each dose and EOT and at any time a subject has any new or worsening respiratory symptoms. Vital signs including temperature, blood pressure, heart rate, respiratory rate. The start and stop time of the study therapy infusions should be documented.

Physical examinations are to be performed at screening. Targeted physical examination should be performed while on treatment and EOT. If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate non-serious or serious adverse event page. During Follow-up visits, targeted physical examination is also required to assess potential late emergent study drug-related AEs.

Except for Cycle 1, Day 1, while on-study the local laboratory assessments at screening should be repeated within 3 days prior to each dose. The hematology, chemistry, and liver function tests will be required at every cycle. Thyroid function testing should be performed every 6 weeks and at EOT. At Screening, thyroid function testing is to include TSH, free T3, and free T4. At subsequent time points, thyroid function testing consists of TSH only. However, if the TSH is abnormal, reflexive testing of free T3 and free T4 are to be performed (Please note that Endocrinopathy Management Algorithm in Appendix 1 of the protocol includes free T4 only if the TSH is abnormal).

Additional measures, including non-study required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug induced liver enzyme evaluations) will be monitored during the follow-up phase via on site/local labs until all study drug-related toxicities resolve, return to baseline, or are deemed irreversible.

Oxygen saturation by pulse oximetry should be obtained prior to each dosing and at any time a subject has any new or worsening respiratory symptoms. A reading at rest and on exertion should be obtained at each time point post-baseline. The extent of the exertion should be based on the judgment of the investigator but should remain consistent for each individual subject throughout the study. If the subject's status changes the investigator can alter the extent of exertion based on their medical judgment. If a subject shows changes on pulse oximetry or other pulmonary-related signs (hypoxia, fever) or symptoms (eg dyspnea, cough, fever) consistent with possible pulmonary adverse events, the subject should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm in the Nivolumab Investigator Brochure and Appendix 1 of this protocol.

Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

Monitoring for AEs in subjects treated with bevacizumab or pemetrexed receiving subjects in Group A, Investigator's Choice chemotherapy (Group C), erlotinib (Group D) and Crizotinib (Group E) should follow recommendations specified in the respective package inserts.

For Group E, the primary objective is safety and tolerability of nivolumab in combination with crizotinib. The AE and SAE occurring during the treatment and follow-up period will be closely monitored.

5.3.1 ECOG Performance Status

ECOG PS will be evaluated and documented at Screening and within 72 hours prior to each dosing visit as outlined in the assessment tables for each group (see Appendix 2 for details of ECOG PS).

5.3.2 Imaging Assessment for the Study

The review of images, assessment of eligibility, response, and resultant treatment decisions for all Groups (A, B, C, D, and E), will be made by the investigators. Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the Study Investigator as per standard medical/clinical judgment.

Any additional imaging that may demonstrate tumor response or progression (including scans performed at unscheduled timepoints and/or at an outside institution) should be collected for RECIST 1.1 tumor assessment.

5.3.3 Electrocardiogram (ECG)

All subjects at screening, are required to have a 12-lead ECG performed during Screening. Subjects in Group E will be required to have a 12-lead ECG at time points following screening as detailed in assessment tables.

Crizotinib is associated with two main cardiac side-effects: QT interval prolongation and bradycardia, therefore 12-lead ECG monitoring will be mandated for Group E patients at baseline,

during treatment (every 8 weeks until first year and every 12 weeks thereafter), EOT, and follow-up visit. See Table 5.1-10 and Table 5.1-11 for details.

The ECG recordings must be analyzed and checked for abnormality by the investigator. Any ECG finding that meets AE criteria should be reported. Positive findings on QT prolongation must be followed up sufficiently as deemed by the investigator. Additional ECGs should be done whenever the investigator deems necessary.

5.4 Efficacy Assessments

Study evaluations will take place in accordance with the tables in Section 5.1, according to RECIST 1.1 criteria.[93] High resolution CT with oral/intravenous contrast or contrast-enhanced MRI is the preferred imaging modalities for assessing radiographic tumor response. If a subject has a known allergy to contrast material, please use local prophylaxis standards to obtain the assessment with contrast if at all possible, or use the alternate modality. In cases where contrast is strictly contraindicated, a non-contrast scan will suffice. Should a subject have a contraindication for CT IV contrast, a non-contrast CT of the chest and a contrast enhanced MRI of the abdomen and pelvis may be obtained. Every attempt should be made to image each subject using an identical acquisition protocol on the same scanner for all imaging time points.

Screening assessments should be performed within 21 days of start of study treatment. In addition to the chest, abdomen, pelvis, all known/suspected sites of disease should be assessed at baseline. Subsequent assessments should include chest, abdomen, and all known/suspected sites of disease using the same imaging method and technique as was used at baseline. Brain MRI is the preferred imaging method for evaluating CNS metastasis, and assessment is required during screening in subjects with a known history of treated/suspected brain metastases. If more than one method is used at screening, then the most accurate method according to RECIST v1.1 should be used when recording data, and should again be used for all subsequent assessments. Bone scan, PET scan, or ultrasound are not adequate for assessment of RECIST response. In selected circumstances where such modalities are the sole modality used to assess certain non-target organs, those non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected. Previously treated CNS metastases are not considered measurable lesions for purposes of RECIST determined response. Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated.

Radiographic tumor assessments will be conducted within 21 days prior to first study dose, at Week 9 (± 1 week) and then every 8 weeks (± 1 week) for up to 2 years. Subjects with a history of brain metastasis may have surveillance MRI approximately every 12 weeks from the date of first dose, or sooner if clinically indicated. In subjects who discontinue the study treatment without evidence of disease progression, the same tumor assessment schedule should be followed. Tumor assessments for all subjects should continue as per protocol even if dosing is interrupted. Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible. Changes in tumor measurements and tumor responses to guide ongoing study

treatment decisions will be assessed by the investigator using RECIST 1.1 (see Appendix 3 for details of RECIST 1.1).

5.4.1 End of Treatment, Follow-up, and Survival Procedures

When treatment is to be discontinued, 1 EOT visit, and 2 follow-up visits will be scheduled. End of Treatment (EOT) visit should be scheduled between 0 - 7 calendar days of last drug administration. If the decision to permanently discontinue the study treatments is taken during a scheduled visit, the EOT visit should be performed instead of the scheduled visit. Follow-up Visit 1 is to occur within 35 days (± 7 days) after the last dose of study treatment, follow-up Visit 2 is to occur within 80 days (± 7 days) of follow-up Visit 1. See Follow-up Tables for specific assessments for each sub-protocol (see Table 5.1-3, Table 5.1-5, Table 5.1-7, Table 5.1-9, and Table 5.1-11). Survival visits will occur approximately every 3 months, beginning from Follow-up Visit 2. Survival will be assessed every 3 months following end of treatment, until death, lost to follow-up, withdrawal of study consent, or for 4 years after the initiation of the study treatment.

Subjects who discontinue study treatment prior to progression, and subjects being treated beyond disease progression, will continue to be followed with radiographic tumor assessments every 8 weeks (± 1 week) for up to 2 years. Radiographic assessments should be performed according to Section 5.4. At documented progression or recurrence, a blood samples will be taken for exploratory assessments of biomarkers.

Survival will be followed after progression, either by direct contact (office visits) or via telephone contact, until death, withdrawal of study consent, or lost to follow-up for 4 years following start of therapy.

For any study Group which is stopped early due to futility, continued treatment of the individual patient on the study will be at the discretion of the investigator. However, once a decision is made to discontinue the study treatment, the end of treatment and 2 follow-up visits are mandated for the safety of the patient. The survival visits are no longer required.

5.4.2 EGFR mutation and ALK translocation assessments

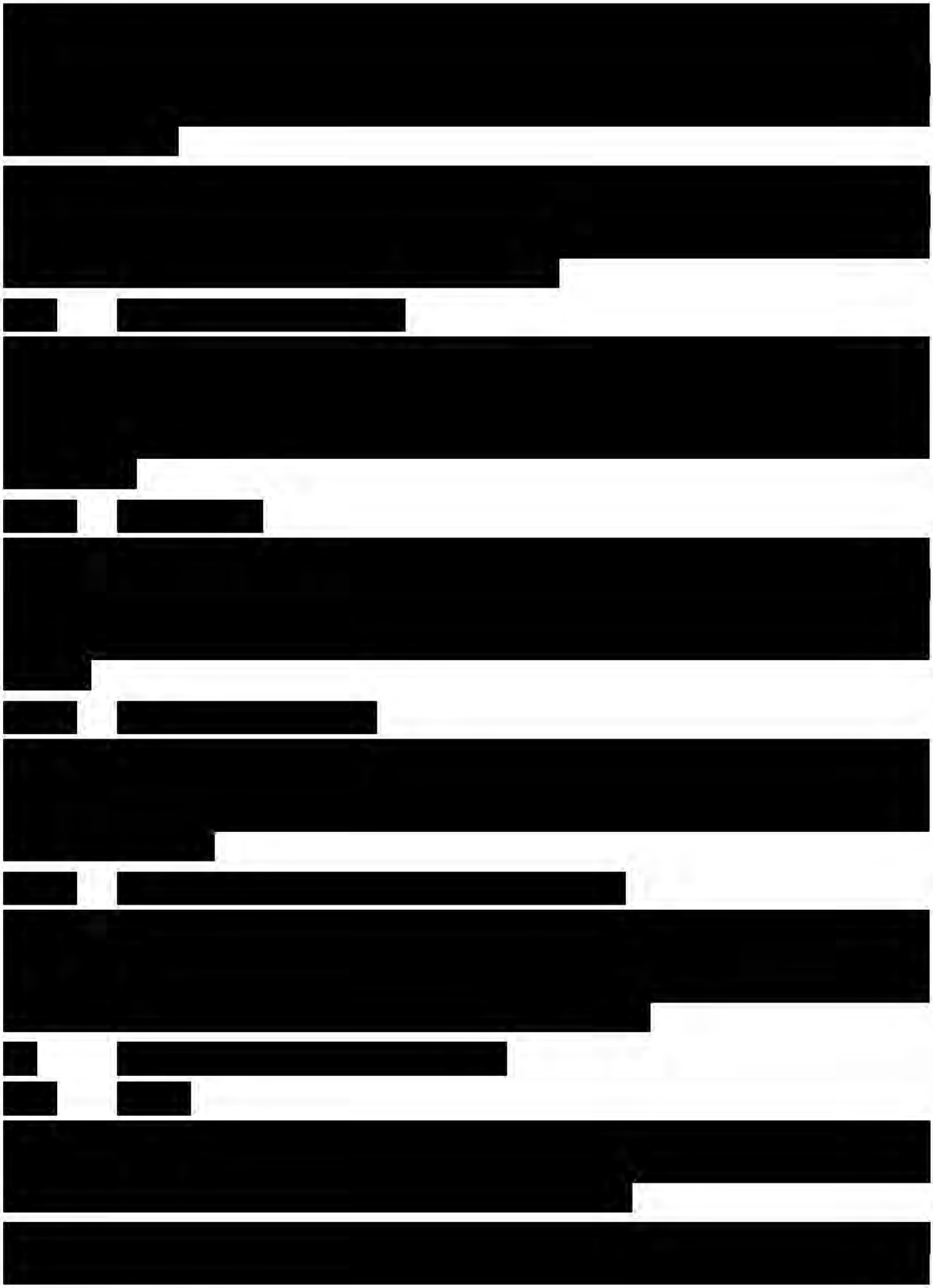
Appropriate documentation of EGFR mutation and ALK translocation tests results must be available before randomization.

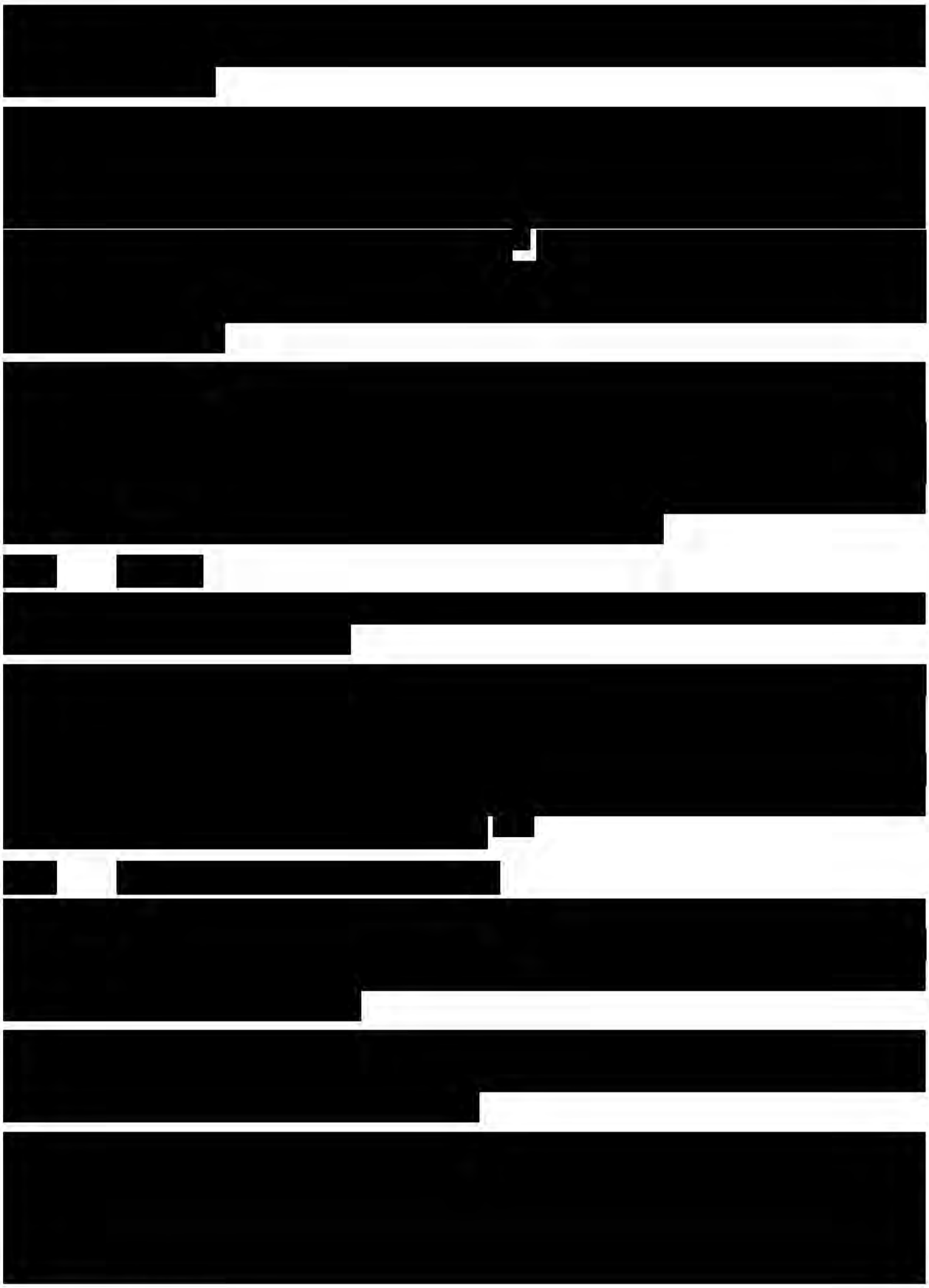
The presence of a common EGFR mutation (Deletion 19 and/or exon 21-L858R substitution or other drug-sensitizing EGFR mutations) is mandatory for the enrollment of Group D patients prior to randomization. The use of an FDA approved assay (ie, cobas® EGFR Mutation Test, therascreen® EGFR RGQ PCR Kit) is strongly encouraged.

The presence of ALK translocation is mandatory for enrollment in Group E. The use of an FDA approved assay (ie, VYSIS ALK Break Apart FISH Probe Kit) is strongly encouraged.

Consult the Medical Monitor regarding the use of EGFR/ALK mutation blood tests.

[redacted]





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6 ADVERSE EVENTS

An **Adverse Event (AE)** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following:

- Related: There is a reasonable causal relationship between study drug administration and the AE.
- Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

6.1 Serious Adverse Events

A **Serious Adverse Event (SAE)** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential DILI is also considered an important medical event. (See Section 6.7 for the definition of potential DILI.)

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential DILI are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 100 days of discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

The investigator should report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours of awareness of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred

method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

SAE Telephone Contact (required for SAE and pregnancy reporting): Refer to Contact Information list.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

Note: All treatment-related SAEs collected on subjects receiving combination therapy must have causality assigned to nivolumab, SOC treatment, or combination therapy by the Investigator.

6.2 Nonserious Adverse Events

A **nonserious adverse event** is an AE not classified as serious.

6.2.1 Nonserious Adverse Event Collection and Reporting

All nonserious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following discontinuation of study treatment.

The collection of nonserious AE information for Groups A, C, D, E and Group B Arm A should begin at initiation of study drug. The collection of nonserious AE information for Group B Am B (Best Supportive Care) should commence at randomization. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects if applicable.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

6.3 Adverse Events of Interest

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, and endocrine abnormalities [adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis]), 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.

Per FDA guidance, IMAE analyses included events, regardless of causality, occurring within 100 days of the last dose. These analyses are limited to subjects who received immunosuppressive medication for treatment of the event, with the exception of endocrine events (hypothyroidism/thyroiditis, hyperthyroidism, hypophysitis, diabetes mellitus, adrenal insufficiency), which were included in the analysis regardless of treatment since these events are often managed without immunosuppression.

Immune-mediated adverse events are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. IMAEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the participant's case report form.

Every adverse event must be assessed by the investigator with regard to whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information will be collected on the participant's case report form.

Table 6.3-1 below provides a summary of the IMAEs category and their respective Preferred Terms.

Table 6.3-1: Preferred Terms Included in Analysis of IMAEs to Support Warning and Precautions

IMAE Category	Preferred Terms included under IMAE Category
Pneumonitis	Pneumonitis, Interstitial lung disease
Diarrhea/Colitis	Diarrhea, Colitis, Enterocolitis
Hepatitis	Hepatotoxicity, Hepatitis, Hepatitis acute, Autoimmune Hepatitis, AST Increased, ALT increased, Bilirubin Increased, ALP increased
Adrenal Insufficiency	Adrenal Insufficiency
Hypothyroidism/Thyroiditis	Hypothyroidism, Thyroiditis

Table 6.3-1: Preferred Terms Included in Analysis of IMAEs to Support Warning and Precautions

IMAE Category	Preferred Terms included under IMAE Category
	Thyroiditis acute (collapsed with thyroiditis for frequency), Autoimmune Thyroiditis (collapsed with thyroiditis for frequency)
Hyperthyroidism	Hyperthyroidism
Hypophysitis	Hypophysitis
Diabetes Mellitus	Diabetes Mellitus, Diabetic ketoacidosis
Nephritis and renal dysfunction	Nephritis, Nephritis allergic, Tubulointerstitial nephritis, Acute renal failure, Renal Failure, Increased Creatinine
Rash	Rash, Rash maculo-papular

IMEAs=immune-mediated adverse events.

6.4 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

6.5 Pregnancy

If, following initiation of the study drug, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with BMS, the pregnant subject may continue study drug after a thorough discussion of benefits and risk with the subject

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours

of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.6 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 6.1.1 for reporting details.).

6.7 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1 for reporting details).

Potential drug induced liver injury is defined as:

1. AT (ALT or AST) elevation > 3 ×ULN
   AND
2. Total bilirubin > 2 ×ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),
   AND
3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

6.8 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

7 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 as pre-specified by the rules that govern the adaptive design, which are described in detail in the statistical analysis plan (SAP).

After meeting, the DMC will notify the clinical study leadership group that it has met and will provide recommendations about the study by telephone or email. Detailed procedures to deliver and address the DMC recommendations are described in the BMS Standard Operating Procedure, which specifies the establishment and operation of clinical trial DMCs. Any recommendation by the DMC regarding study modification will be submitted to the clinical study leadership team within pre-specified business days of the DMC meeting.

The oncology therapeutic area of BMS has primary responsibility for design and conduct of the study. Details of DMC responsibilities and procedures will be specified in the DMC charter.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

8.1.1 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 8.1.1-1. The sample size for each Group depends on the population, treatment effect, and primary endpoint for each group.

Table 8.1.1-1: Maximum Sample Size and Comparisons of Interest

Population	Maximum Sample Size	Primary Endpoint	Comparisons of interest
Group A: Maintenance, NSQ, PS 0-1, $EGFR_{wt}$ and ALK_{wt}	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, $EGFR_{mut}$	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 patients 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.

8.1.2 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 8.1.2-1. 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 8.1.2-1: 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.

8.2 Populations for Analyses

Efficacy will be analyzed for all randomized patients (except Group E for treated patients) and safety for all treated patients. Population for each Group is summarized briefly below.

Group A:

- Subjects who have completed at least 4 cycles (up to 6 cycles) of bevacizumab, carboplatin or cisplatin, and paclitaxel
  - Subjects who have completed at least 4 cycles (up to 6 cycles) of pemetrexed and carboplatin or cisplatin, and without disease progression.

Group B:

- Subjects with histologically confirmed Stage 4 or recurrent locally advanced SQ NSCLC. Enrolled subjects must have completed at least 4 cycles (up to 6 cycles) of SOC chemotherapy, and without disease progression.

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.

Group E:

- First-line treatment for subjects with histologically confirmed Stage 4 or recurrent locally advanced ALK-positive NSCLC.

8.3 Endpoints

- 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, FACT-L, and ActiGraph 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.

8.3.1 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.

8.3.2 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]

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

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

8.4.2 Efficacy Analyses

8.4.2.1 Efficacy Analysis for Group A: Maintenance, NSQ PS 0-1, $EGFR_{wt}$ and ALK_{wt}

This group will enroll 2 subject cohorts, subjects who have completed at least 4 cycles of 1) bevacizumab, carboplatin or cisplatin, and paclitaxel or 2) pemetrexed and carboplatin or cisplatin. Within each subject cohort, subjects will be randomized 1:1:1 to either 1) SOC maintenance therapy 2) nivolumab alone or 3) nivolumab plus SOC maintenance therapy. PFS and OS are co-primary endpoints.

The OS curves for each treatment group will be estimated using the Kaplan-Meier (KM) product-limit method. Two-sided, 95% confidence intervals for median OS will be computed by Brookmeyer and Crowley method.

The subjects may be followed for survival up to 4 years. Survival rates at 6, 12, 18, 24, and up to 4 year will also be estimated using KM estimates on the OS curve for each randomized arm. Associated two-sided 95% CIs will be calculated using the Greenwood's formula.

PFS will be summarized similarly as OS.

ORR will be computed in each treatment group along with the exact 95% CI using the Clopper-Pearson method. BOR will be summarized by response category for each treatment group. A by subject listing of BOR and Tumor Measurements will be provided.

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

8.4.2.2 Efficacy Analysis for Group B: Maintenance, SQ, PS 0-1

The efficacy analysis for Group B will be same as the efficacy analysis for Group A.

8.4.2.3 Efficacy Analysis for Group C: First-line NSQ and SQ, PS 2, $EGFR_{wt}$ and ALK_{wt}

The efficacy analysis for Group C will be same as the efficacy analysis for Group A.

8.4.2.4 Efficacy Analysis for Group D: First-line, PS 0-2, EGFRmut

The efficacy analysis for Group D will be similar to the efficacy analysis for Group A. In addition, DCR, which is not evaluated in Group A, will be computed in each treatment group along with the exact 95% CI using the Clopper-Pearson method.

8.4.2.5 Efficacy Analysis for Group E: First-line, PS 0-2, ALK-positive

The OS and PFS curves will be estimated using the Kaplan-Meier (KM) product-limit method.

A by subject listing of BOR and Tumor Measurements will be provided.

8.4.3 Safety Analyses

All safety data will be summarized and listed for all treated subjects. All AEs, SAEs, treatment-related AEs, and treatment-related SAEs will be summarized using 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.

Descriptive statistics of safety (AE and lab data) including incidence, median values using the Kaplan-Meier product-limit method with 95% CI using the Brookmeyer and Crowley method of time to onset and time to resolution, and rate of discontinuation due to event occurrence will be presented for all treated subjects. Time to onset is calculated from first dosing date to the event onset date. If a subject never experienced the given AE, the subject will be censored at the last contact date. Time to resolution is calculated from the AE onset date to AE end date. If an AE is ongoing at the time of analysis, the time to resolution will be censored at the last contact date.

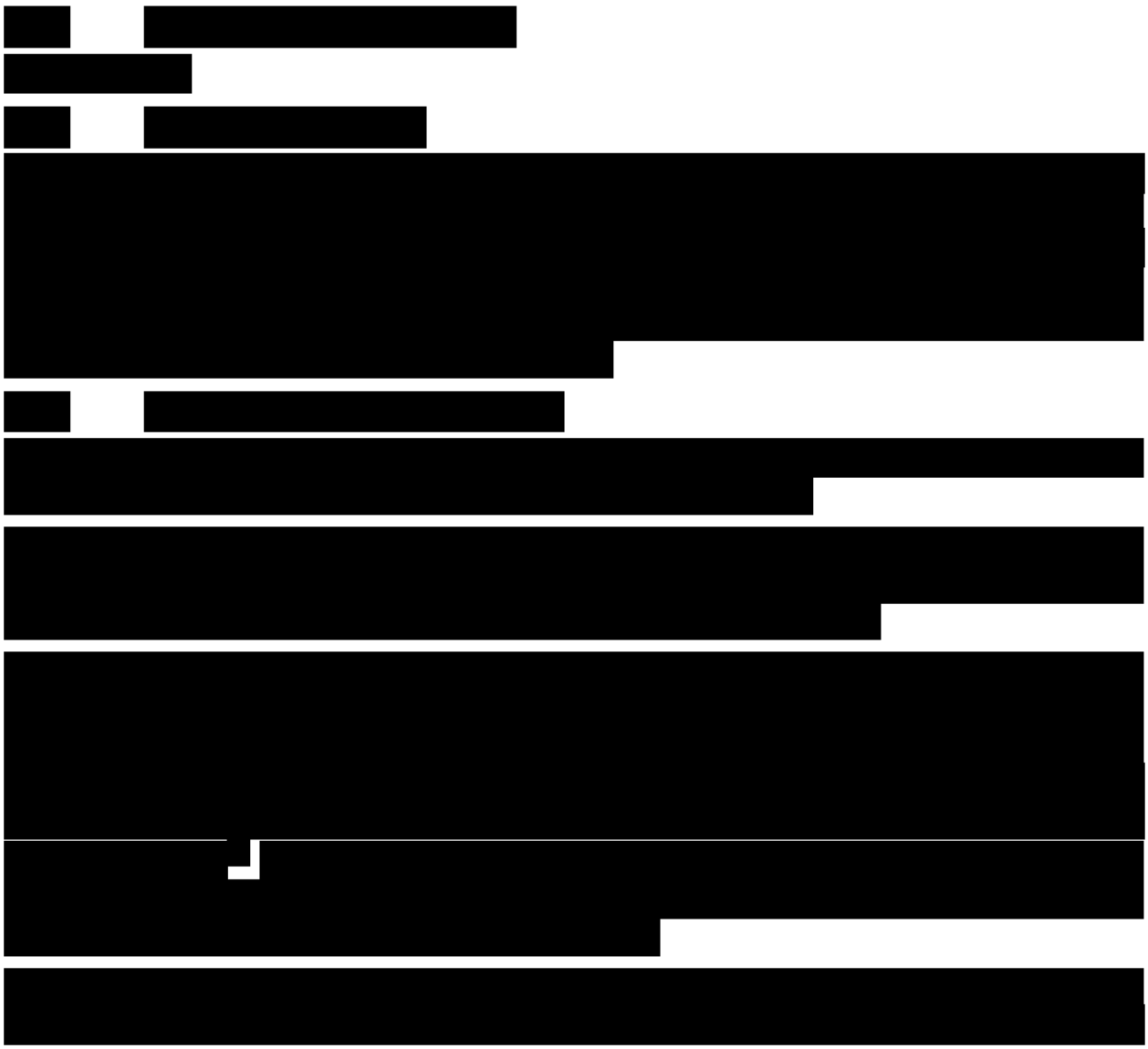
Frequency, management and resolution of IMAEs are to be analyzed. A tabular of the incidence of overall IMAEs (by preferred term) and serious IMAEs will be performed. A descriptive analysis of IMAEs including time-to-onset, severity, duration, action taken with the study drug, dosing delays of the study drug, corticosteroid details, re-challenge information and outcome of the AE are individually characterized in the following subsections:

- pneumonitis IMAEs

- diarrhea/colitis IMAEs
- hepatitis IMAEs:
- nephritis and renal dysfunction IMAEs
- rash IMAEs
- endocrine IMAEs by subcategories including adrenal insufficiency, hypophysitis, hypothyroidism/thyroiditis, hyperthyroidism, and diabetes.

For Group E, the primary objective is safety and tolerability of nivolumab in combination with crizotinib. The primary objective will be measured by:

1) Frequency of adverse events occurring up to 100 days after the last dose of study drug
2) Frequency of serious adverse events occurring up to100 days after the last dose of study drug
3) Frequency of clinical laboratory test by worst toxicity grade (as assessed at screening and every cycle).



[redacted]

8.5 Interim Analyses

At the time of Amendment 4, one safety interim analysis was conducted. Due to early closure of the enrollment for Groups A, B, C, and E, no further interim analysis is planned for these groups.

8.5.1 Interim Analyses for Group D

Safety interim analyses are planned for Group D approximately yearly.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion BMS
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

BMS representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On-site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the

facilities remain acceptable. Certain CRF pages and/or electronic files may serve as the source documents.

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.

9.1.2.1 Source Documentation

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

9.1.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to BMS.

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of study drug (inventoried and dispensed) is maintained at the study site to include investigational product and the following non-investigational product(s): Gemcitabine, pemetrexed, paclitaxel, Nab-paclitaxel, carboplatin, bevacizumab, etc. Records or logs must comply with applicable regulations and guidelines and should include:

- Amount received and placed in storage area
- Amount currently in storage area
- Label identification number or batch number
- Amount dispensed to and returned by each subject, including unique subject identifiers
- Amount transferred to another area/site for dispensing or storage
- Non-study disposition (eg, lost, wasted)
- Amount destroyed at study site, if applicable
- Amount returned to BMS (for nivolumab)
- Retain samples for bioavailability/bioequivalence, if applicable
- Dates and initials of person responsible for investigational product dispensing/accountability, as per the delegation of authority form.

BMS will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paper or electronic SAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and

who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected as appropriate based on the following criteria:

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee
- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTA) governing [Study site or Investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to BMS at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	If one form of contraception is required, Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. If two forms of contraception is required, Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. **Expanded definition** Complete abstinence as defined as complete avoidance of heterosexual intercourse is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the subject. This does not mean periodic abstinence (eg, calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence

11 LIST OF ABBREVIATIONS

Term	Definition
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 a day
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
EBUS	Endobronchial Ultrasound

Term	Definition
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEG	Electroencephalogram
Eg	exempli gratia (for example)
EGFR	Epidermal Growth Factor Receptor
EQ-5D	EuroQoL Five Dimension
FACT-L	Functional Assessment of Cancer Therapy-Lung
FDA	Food and Drug Administration
FISH	fluorescent in-situ hybridization
FSH	follicle stimulating hormone
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	id est (that is)
IEC	Independent Ethics Committee
ILD	interstitial lung disease
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
IRB	Institutional Review Board

Term	Definition
IHC	Immunohistochemistry
IU	International Unit
IV	Intravenous
IWRS	Interactive web response system
Kg	Kilogram
LCSS	Lung Cancer Symptom Scale
LDH	lactate dehydrogenase
LFT	liver function test
MET	Metabolic equivalents
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 of subjects or observations
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

Term	Definition
PO	By mouth
PPK	population pharmacokinetic
PR	Partial response
PRES	posterior reversible encephalopathy syndrome
PRO	Patient-reported outcomes
PS	Performance status
QD	Every day
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
SQ	Squamous
TCR	T-cell receptor
T-HALF	Half life
TILs	tumor-infiltrating lymphocytes
TKI	Tyrosine-kinase inhibitor
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/

APPENDIX 2 ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS [a]	
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

[redacted]

APPENDIX 3 RECIST 1.1 CRITERIA

This Appendix has been excerpted from the full RECIST 1.1 criteria. For information pertaining to RECIST 1.1 criteria not contained in the study protocol or in this Appendix, please refer to the full publication.[8]

1 ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion.

1.1 Measurability of tumor

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Measurable lesions must be accurately measured in at least one dimension (longest diameter in the plane of the measurement to be recorded) with a minimum size of:

- 10 mm by CT scan - (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest x-ray
- Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

All measurements should be recorded in metric notation, using calipers if clinically assessed.

Special considerations regarding lesion measurability

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not beconsidered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Non-measurable lesions are all other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as non-measurable lesions. Lesions considered non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

1.2 Method of assessment

The **same method of assessment and the same technique should be used** to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be performed rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT scan is based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

Chest x-ray: Chest CT is preferred over chest x-ray, particularly when progression is an important endpoint, since CT is more sensitive than x-ray, particularly in identifying new lesions.

However, lesions on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response.

2 BASELINE DOCUMENTATION OF 'TARGET' AND 'NON-TARGET' LESIONS

Target lesions: When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and should lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should not be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or 'unequivocal progression'. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

3 TUMOR RESPONSE EVALUATION AND RESPONSE CRITERIA

3.1 Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an

absolute increase of at least 5 mm. Note: the appearance of one or more new lesions is also considered progression.

Stable Disease (SD): Neither sufficient shrinkage from the baseline study to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Special notes on the assessment of target lesions

- **Lymph nodes:** Lymph nodes identified as target lesions should always have the actual short axis measurement recorded and should be measured in the same anatomical plane as the baseline examination, even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.
- **Target lesions that become 'too small to measure' :** All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). If the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

However, when such a lesion becomes difficult to assign an exact measure to then:

1) if it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
2) if the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (note: in case of a lymph node believed to be present and faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).

Lesions that split or coalesce on treatment: When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

3.2 Evaluation of non-target lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

- The concept of progression of non-target disease requires additional explanation as follows:
- *When the patient also has measurable disease*: To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.
- *When the patient has only non-measurable disease:* To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point.

3.3 New lesions

The appearance of new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be constitute PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents new disease. If repeat scans confirm that there is a new lesion, then progression should be declared using the date of the initial scan.

3.4 Tumor markers

Tumor markers alone cannot be used to assess objective tumor responses. If markers are initially above the upper normal limit, however, they must normalize in order for a patient to be considered as having attained a complete response.

4 EVALUATION OF BEST OVERALL RESPONSE

4.1 Time point response

A response assessment should occur at each time point specified in the protocol.

For patients who have measurable disease at baseline Appendix Table 1 provides a summary of the overall response status calculation at each time point.

Table 1: Appendix Table 1 -Summary of the Overall Response Status Calculation [Time point response -patients with target (+/-) non-target disease]

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR=complete response, PR=partial response, SD=stable disease, PD=progressive disease, and NE=inevaluable

4.2 Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

4.3 Best overall response: all timepoints

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol. In this circumstance, the best overall response can be interpreted as in Appendix Table 2.

Table 2: Appendix Table 2 -Best overall response when confirmation of CR and PR required

Overall Response First Timepoint	Overall Response Subsequent Timepoint	Best Overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR=complete response, PR=partial response, SD=stable disease, PD=progressive disease, and NE=inevaluable

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

4.4 Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Appendix Table 1 and Table 2.

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at

the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

5 ADDITIONAL CONSIDERATIONS

5.1 Duration of response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

5.2 Lesions that disappear and reappear

If a lesion disappears and reappears at a subsequent time point it should continue to be measured. However, the patient's response at the point in time when the lesion reappears will depend upon the status of his/her other lesions. For example, if the patient's tumour had reached a CR status and the lesion reappeared, then the patient would be considered PD at the time of reappearance.

In contrast, if the tumour status was a PR or SD and one lesion which had disappeared then reappears, its maximal diameter should be added to the sum of the remaining lesions for a calculated response: in other words, the reappearance of an apparently 'disappeared' single lesion amongst many which remain is not in itself enough to qualify for PD: that requires the sum of all lesions to meet the PD criteria. The rationale for such a categorization is based upon the realization that most lesions do not actually 'disappear' but are not visualized because they are beyond the resolving power of the imaging modality employed.

5.3 Use of FDG-PET

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

1) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion. Confirmatory CT is recommended.
2) No FDG-PET at baseline and a positive FDG-PET at follow-up:
   a) If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

b) If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).

c) If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.