Official Title of Study:

Open-Label, Randomized Trial of Nivolumab (BMS-936558) plus Pemetrexed/Platinum or Nivolumab plus Ipilimumab (BMS-734016) vs Pemetrexed plus Platinum in Stage IV or Recurrent Non-Small Cell Lung Cancer (NSCLC) Subjects with Epidermal Growth Factor Receptor (EGFR) Mutation Who Failed 1L or 2L EGFR Tyrosine Kinase Inhibitor Therapy

CheckMate 722: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 722

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Protocol Number: CA209722
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Clinical Protocol CA209722

Open-Label, Randomized Trial of Nivolumab (BMS-936558) plus Pemetrexed/Platinum or Nivolumab plus Ipilimumab (BMS-734016) vs Pemetrexed plus Platinum in Stage IV or Recurrent Non-Small Cell Lung Cancer (NSCLC) Subjects with Epidermal Growth Factor Receptor (EGFR) Mutation Who Failed 1L or 2L EGFR Tyrosine Kinase Inhibitor Therapy

CheckMate 722: **CHECK**point pathway and nivolu**MA**b clinical **T**rial **E**valuation 722

Revised Protocol 06

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 06	30-Jul-2020	• Updated name and contact information of the Study Director on the title page. • Replaced "assess" with "compare" for the primary objective of PFS and "determine" with "compare" for the first secondary objective of OS. • Updated the total number of subjects randomized in the study and revised the number of subjects randomized to Arm A and Arm C in the study design (synopsis and body text and study schematic). • Added an overall rationale for the amended protocol outlining the revised number of subjects enrolled and the statistical analyses for progression free survival (PFS) based on newly available external data (IMpower150), with details included in Section 1.1.12. Added the corresponding reference with a link to Section 12. • Added myocarditis to the list of Grade 3 adverse events for nivolumab dose discontinuation in Section 4.5.7.1 and added the algorithm to Appendix 2. • Removed reference to an additional 1 year treatment with nivolumab or nivolumab plus ipilimumab and the associated guidelines in Section 4.5.9; updated study design to reflect change. Removed sentence referring to Table 5.1-2. • Due to enrollment challenges and newly available data demonstrating adequate power to evaluate improvement in PFS, the statistical analysis section was revised to align with the revised number of subjects. • Revised sample size and statistical assumptions in Table 8.1-1 • Removed Table 8.1-2 and text justifying statistical power for the overall survival (OS) comparison between Arm A and Arm C. • Removed references to an interim analysis of OS in Sections 8.4 and 8.4.2. • Other typographical/editorial changes throughout including a date change to the algorithms in Appendix 2.
Revised Protocol 05	22-Mar-2019	• Updated study title
Revised Protocol 04	20-Nov-2018	• Stopped enrollment to Arm B (nivolumab + ipilimumab) • Moved PFS, OS, ORR and DoR of nivolumab + ipilimumab vs chemotherapy to exploratory objectives • Allowed enrollment of subjects with prior use of osimertinib as 1L and 2L • Allowed randomization of subjects with asymptomatic CNS metastases and treatment of CNS metastases during the screening period. • Added stratification by prior use of osimertinib • Allowed local laboratory testing of T790M mutation in subjects who progressed on 1L first- or second-generation EGFR TKI

Document	Date of Issue	Summary of Change
		• Updated statistical section to align with updated study design • Updated Appendices to align with program standards • Updated study personnel
Administrative Letter 02	09-Aug-2017	Updated study personnel
Administrative Letter 01	06-Jul-2017	Added EUDRACT Number
Revised Protocol 03	04-Apr-2017	Incorporates Amendment 03
Amendment 03	04-Apr-2017	• Added a maximum treatment duration of 24 months to the nivolumab and nivolumab and ipilimumab arms of this trial. • Added Live vaccines as a prohibited treatments • Added caution to concomitantly administering NSAIDs and pemetrexed • Clarified the switch from carboplatin to cisplatin at the investigator's discretion if the subject has discontinued cisplatin alone. • The hierarchical testing order of progression-free survival, overall survival, and objective response rate was clarified. • Added clarity for the investigational products in China
Revised Protocol 02	15-Aug-2016	Incorporates Amendment 02
Amendment 02	15-Aug-2016	• Adds smoking history as a stratification factor • Changes the language describing when PD-L1 expression is not known • Increases the window from randomization to first dose from 3 days to 7 days. • CNS metastasis criteria were changed. • Adds a safety review by the Data Monitoring Committee for the first 15 patients from Asian sites after receiving treatment for at least 3 months • Aligns the protocol to the nivolumab program standards, including changes to the contraception language.
Revised Protocol 01	20-Jun-2016	Incorporates Amendment 01
Amendment 01	20-Jun-2016	• The sample size and statistical analyses sections have been updated using a 2-sided log-rank test to reflect the registrational nature of this trial. • Response to tyrosine kinase inhibitor (TKI) therapy has been removed as a stratification factor. • The presence or absence of brain metastases has been added as a stratification factor.
Original Protocol	28-Apr-2016	Not applicable

OVERALL RATIONALE FOR REVISED PROTOCOL 06:

Enrollment in the CA209722 study was slow and was further impacted by the COVID-19 pandemic, making it difficult to reach the planned sample size for this study in a timely manner. Accordingly, enrollment in this study was stopped in June, 2020.

Based on currently available external data from IMpower150, at least 3-months improvement in PFS was observed in a limited number of subjects following atezolizumab (an anti-PD-L1 agent) plus chemotherapy (n = 34) as compared with chemotherapy (n = 45). Given the limited sample size of IMpower150, it is reasonable to predict that the addition of nivolumab to SOC chemotherapy may provide clinically meaningful improvement of 2 months in PFS. Therefore, the statistical assumption in this study was revised to 2-months improvement in PFS with delay in separation of curves. With the revised assumptions, sample size of approximately 135 subjects per arm (Arm A and Arm C) will provide 83% power to detect an average HR of 0.692 with a significance level of 0.05. The statistical analysis section has been revised to account for the revised assumptions.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title page	Replaced the name of the Study Director	Revised to reflect a change in personnel.
Synopsis Objectives, Section 1.3.1 Primary Objective, and Section 1.3.2 Secondary Objective	• Replaced “assess” with “compare” for the primary objective of PFS • Replaced “determine” with “compare” for the first secondary objective of OS	To simplify the wording for clarity.
Synopsis Study Design, Section 3.1 Study Design and Duration, and Synopsis Statistical Considerations	• Updated the total number of subjects randomized in in Arms A and C • Revised the study design schematic in both sections • Revised the number of subjects and number of events analyzed for PFS (primary objective) and associated power for PFS and OS • Deleted reference to an interim analysis for OS	Due to enrollment challenges and based on newly available external data, the statistical assumptions for the sample size calculation were revised for the PFS endpoint.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 1.1.12 Rationale for Reducing Sample Size	Added section	Due to enrollment challenges and based on newly available external data, the statistical assumption for the sample size calculation was changed for the PFS endpoint.
Section 4.5.7.1 Nivolumab Dose Discontinuation	Myocarditis was added to the list of Grade 3 AEs.	For consistency with the AE profile of nivolumab per the Investigator's Brochure (version 18).
Section 4.5.9 Nivolumab and Ipilimumab Duration of 24 Months	• Removed reference to treating subjects with disease progression or recurrence and the associated guidelines. • Removed sentence referring to Table 5.1-2	Consistent with updated treatment duration of nivolumab-containing regimens (at the program level), reference to treating subjects with disease progression or recurrence as continued treatment beyond 24 months is no longer offered. Reference to continued treatment and the associated guidelines have been deleted.
Section 8.1 Sample Size Determination	• Reduced the number of subjects and number of events to recalculate the power statistics for PFS (primary objective) • Removed original sample size and power associated with OS and modified to hierarchical testing and 10% power. • Revised Table 8.1-1 Sample Size Justification for PFS Comparison	Due to enrollment challenges and based on newly available external data, the statistical assumption for the sample size calculation was changed for the PFS endpoint.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
	• Removed Table 8.1-2 Sample Size Justification for OS Comparison	
Section 8.4	Removed reference to interim analyses of OS data.	To make consistent with the revisions in sample size determination requirements.
Section 8.4.2 Efficacy Analyses	Removed reference to multiple OS analyses.	To make consistent with the revisions in sample size determination requirements.
Section 8.5 Interim Analysis	Removed description of interim analysis and replaced with a statement that no interim analyses are planned.	To make consistent with the revision in sample size determination.
Section 12 References	Added reference 33 Reck M, et al.	IMpower150 data referenced in rationale for revision of sample size and power calculations.
Appendix 2	Added myocarditis algorithm and updated date on Appendix 2.	For consistency with the AE profile of nivolumab per the Investigator's Brochure (version 18).
All	Minor typographical/editorial corrections	Minor, therefore have not been summarized.

SYNOPSIS

Clinical Protocol CA209722

Protocol Title: Open-Label, Randomized Trial of Nivolumab (BMS-936558) plus Pemetrexed/Platinum or Nivolumab plus Ipilimumab (BMS-734016) vs Pemetrexed plus Platinum in Stage IV or Recurrent Non-Small Cell Lung Cancer (NSCLC) Subjects with Epidermal Growth Factor Receptor (EGFR) Mutation Who Failed 1L or 2L EGFR Tyrosine Kinase Inhibitor Therapy

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s):

- Arm A: Nivolumab 360 mg IV, followed by pemetrexed (500 mg/m^2) with cisplatin (75 mg/m^2) OR Nivolumab 360 mg IV, followed by pemetrexed (500 mg/m^2) with carboplatin (AUC 5 or 6).
- Arm B: Nivolumab 3 mg/kg IV will be administered every 2 weeks and ipilimumab 1 mg/kg IV will be administered every 6 weeks.
- NOTE: As per revised protocol 04, Arm B has closed enrollment.
- Arm C: Pemetrexed (500 mg/m^2) with cisplatin (75 mg/m^2) administered on Day 1 of each cycle OR Pemetrexed (500 mg/m^2) with carboplatin (AUC 5 or 6).

Study Phase: 3b

Research Hypothesis: In subjects with EGFR mutation (ie, G719X, L861Q, Del 19, and L858R), non-small cell lung cancer (NSCLC) whose tumor has progressed on first-line (1L) or second-line (2L) EGFR TKIs, concurrent administration of nivolumab plus pemetrexed/platinum has superior efficacy defined by progression-free survival (PFS) to pemetrexed/platinum alone.

Objectives:

Primary

- To compare the PFS by blinded independent central review (BICR) of nivolumab plus pemetrexed/platinum to pemetrexed plus platinum in EGFR mutation positive (ie, G719X, L861Q, Del 19, and L858R), metastatic or recurrent NSCLC whose tumor has progressed on 1L or 2L EGFR TKIs
- *Secondary*
- To compare the OS of nivolumab plus pemetrexed/platinum to pemetrexed plus platinum in EGFR mutation positive (ie, G719X, L861Q, Del 19, and L858R), metastatic or recurrent NSCLC whose tumors have progressed on 1L or 2L EGFR TKI
- To determine the objective response rate (ORR) per RECIST 1.1 by BICR, the duration of response (DOR) by BICR, and the 9-month and 12-month PFS rates by BICR of nivolumab plus pemetrexed/platinum compared to pemetrexed plus platinum in EGFR mutation positive (ie, G719X, L861Q, Del 19, and L858R), metastatic or recurrent NSCLC that has progressed on 1L or 2L EGFR TKI

Exploratory

- To assess the PFS by BICR, ORR (per RECIST 1.1) by BICR, DOR by BICR, and OS by PD-L1 status (≥ 1%, < 1%/not evaluable/indeterminate membranous staining in tumor cells) in subjects treated with nivolumab plus pemetrexed/platinum compared to pemetrexed plus platinum
- To assess the safety and tolerability of nivolumab plus pemetrexed/platinum compared to pemetrexed plus platinum in EGFR mutation positive (ie, G719X, L861Q, Del 19, L858R), metastatic or recurrent NSCLC that has progressed on 1L or 2L EGFR TKI

[redacted]

[redacted]

- To assess health-related quality of life using the EQ-5D-3L and LCSS
- To evaluate ORR by BICR, DOR by BICR, PFS by BICR and OS of nivolumab plus ipilimumab in EGFR mutation positive (ie, G719X, L861Q, Del 19, and L858R), T790M negative, metastatic or recurrent NSCLC that has progressed on 1L EGFR TKI
- To evaluate PFS after next line of therapy (PFS2) of nivolumab plus pemetrexed/platinum vs. pemetrexed plus platinum in EGFR mutation positive (ie, G719X, L861Q, Del 19, L858R), metastatic or recurrent NSCLC

Study Design:

This is an open-label, randomized, Phase 3 study in subjects with EGFR mutation, metastatic or recurrent NSCLC whose tumors have progressed on 1L or 2L EGFR TKI.

In revised protocol 03, subjects were randomized to 3 arms in a 1:1:1 ratio. Subjects were stratified by PD-L1 expression (≥ 1% or < 1%/not evaluable/indeterminate), by presence or absence of brain metastases, and by smoking history (current/former or never smoker).

Revised protocol 04 stopped enrollment in Arm B (nivolumab plus ipilimumab) but continued to randomize eligible subjects into either nivolumab plus platinum doublet chemotherapy arm (Arm A) or platinum doublet chemotherapy arm (Arm C) in a 1:1 ratio. Randomization to Arm A or Arm C was stratified by PD-L1 expression (≥ 1% or < 1%/not evaluable/indeterminate), brain metastases (presence or absence), smoking history (current/former or never smoker) and prior osimertinib use (yes or no). Approximately 500 subjects were planned to be randomized to Arms A or C. Subjects already randomized in Arm B of nivolumab plus ipilimumab remained on treatment at the discretion of the investigator.

Revised protocol 05 updated the study title to align with the updated study design in revised protocol 04.

Revised protocol 06 adjusts assumptions for PFS endpoint based on external data and revises the number of subjects randomized to Arm A and Arm C to approximately 270 in total for statistical analysis of the PFS endpoint. The statistical plan is revised for the PFS and OS endpoints.

PD-L1 expression will be assessed in tumor cells, using 1% as the expression level and categorized into 2 separate groups (≥ 1% or < 1%/not evaluable/indeterminate). PD-L1 status will be determined by immunohistochemical (IHC) staining of PD-L1 protein in the submitted tumor sample and categorized as follows:

- PD-L1 positive - defined as ≥ 1% tumor cell membrane staining positive in a minimum of 100 evaluable tumor cells
- PD-L1 negative – defined as < 1% tumor cell membrane staining positive in a minimum of 100 evaluable tumor cells
- PD-L1 not evaluable/indeterminate- defined as subjects with insufficient quantity tumor biopsy specimens for IHC staining and analysis or subjects with tumors that are unable to determine the PD-L1 status, despite appropriate amount of tissue sample. For subjects with PD-L1 not evaluable/indeterminate tumors, key efficacy and safety parameters will be summarized and grouped with PD-L1 negative subjects. Enrollment in this stratum will be capped to 10% of subjects.

Screening begins by establishing the subject's initial eligibility and signing of the informed consent (ICF). Subjects must be randomized within 42 days of signing the ICF unless otherwise noted. Tumor tissue (archival [slides preferably within 6 months before first dose of study drug] or fresh tumor biopsy) must be submitted to a third party vendor for determination of PD-L1 status.

For subjects who failed 1L first- or second-generation TKI, T790M testing will be conducted on tumor tissue (either at local laboratory with an approved test or at central laboratory) and only subjects with T790M negative status will be randomized. For subjects who failed osimertinib, T790M testing is not required.

The subject is randomly assigned to Arm A or Arm C. Enrollment to Arm B is stopped as of revised protocol 04. Study treatment must begin within 7 days of randomization.

Arm A: Nivolumab plus Platinum-doublet Chemotherapy (Each Cycle = 21 days [3 weeks])

- Nivolumab will be administered IV every 3 weeks with platinum-doublet chemotherapy IV for a maximum of 4 cycles.
- Nivolumab 360 mg IV, followed by pemetrexed (500 mg/m^2) with cisplatin (75 mg/m^2) administered on Day 1 of each cycle
- OR
- Nivolumab 360 mg IV, followed by pemetrexed (500 mg/m^2) with carboplatin (AUC 5 or 6) administered on Day 1 of each cycle

Following completion of the fourth cycle of nivolumab/chemotherapy, all subjects who have not experienced disease progression should continue nivolumab 360 mg IV and pemetrexed (500 mg/m^2) every 3 weeks until the progression of disease, discontinuation due to toxicity, withdrawal of consent, or study closure. Nivolumab should only be administered for a maximum of 24 months (96 weeks) from the first study treatment.

Arm B: Nivolumab plus Ipilimumab (Each Cycle = 14 day [2 weeks])

- Nivolumab 3 mg/kg IV will be administered every 2 weeks and ipilimumab 1 mg/kg IV will be administered every 6 weeks until the progression of disease, discontinuation due to toxicity, withdrawal of consent, a maximum of 24 months (96 weeks) from the first study treatment, or study closure.

NOTE: As per revised protocol 04, Arm B has closed enrollment.

Arm C: Platinum Doublet Chemotherapy (Each Cycle = 21 days [3 weeks])

Platinum-doublet chemotherapy is administered IV in 3-week cycles for up to a maximum of 4 cycles.

- Pemetrexed (500 mg/m^2) with cisplatin (75 mg/m^2) administered on Day 1 of each cycle
- OR
- Pemetrexed (500 mg/m^2) with carboplatin (AUC 5 or 6) administered on Day 1 of each cycle.

Subjects who have stable disease or response after 4 cycles of pemetrexed with cisplatin or carboplatin should continue pemetrexed alone as maintenance therapy until disease progression or unacceptable toxicity.

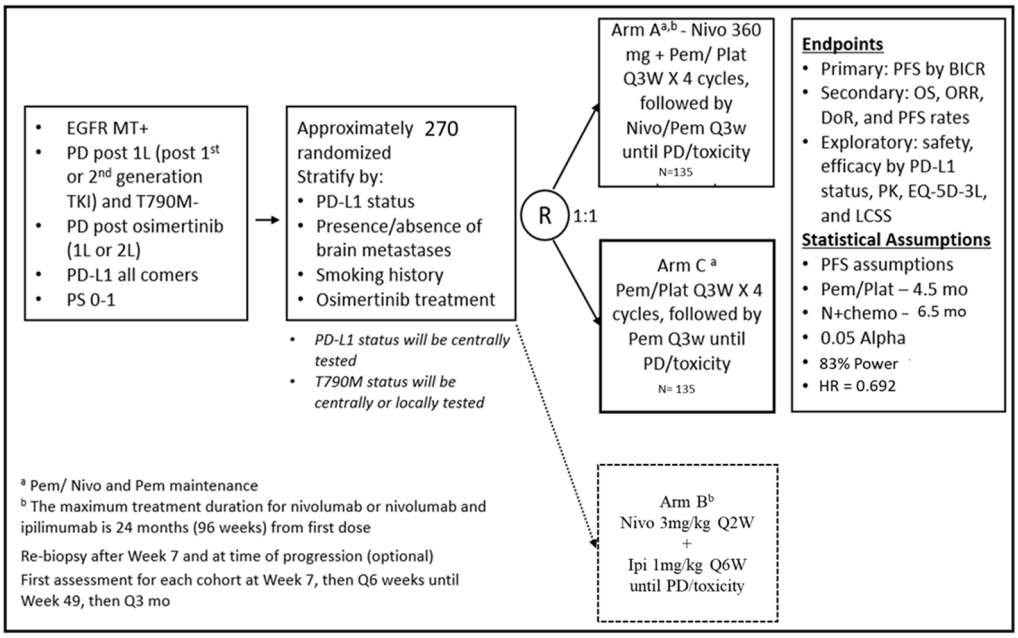
All Arms

Subjects will be assessed for response by CT or MRI beginning at Week 7 (± 7 days), every 6 weeks (± 7 days) until Week 49, and then every 12 weeks (± 7 days) until progression, study treatment discontinuation, or the start of the subsequent anti-cancer therapy, whichever occurs later. Tumor assessments must continue per protocol until RECIST 1.1 progression is confirmed by BICR. OS will be followed continuously while subjects are on the study drugs and every 3 months via in-person or phone contact after a subject discontinues the study drugs.

The Follow-Up Phase begins when the decision to discontinue a subject from all treatment, including maintenance, is made.

Subjects will be followed for drug-related toxicities until these toxicities resolve, return to baseline, or are deemed irreversible. All adverse events will be documented for a minimum of 100 days after the last dose of study medication.

After completion of the first 2 follow-up visits, subjects will be followed every 3 months for survival. Survival follow-up visits may be performed by phone contact or office visit.



Study Population:

Inclusion:

a) Eastern Cooperative Group (ECOG) Performance Status 0-1

b) Subjects with histologically confirmed Stage IV or recurrent EGFR-mutated (ie, G719X, L861Q, Del 19, and L858R) NSCLC (per the 7th International Association for the Study of Lung Cancer classification) with disease progression on one or two prior lines of treatment with EGFR TKIs (allowed TKIs must be approved by the local health authority, including but not limited to erlotinib, gefitinib afatinib, dacomitinib, and osimertinib).

c) No evidence of exon 20 T790M mutation obtained at progression on prior first- or second-generation EGFR TKI therapy. Initial testing of blood samples is allowed in local laboratories using assays approved by local Health Authority only to rule out T790M-positive subjects. T790M negative status must be confirmed by a central or a local laboratory using the cobas® EGFR Mutation Test v2 (US-IVD) on tissue samples in patients failing first- or second-generation TKIs. In osimertinib treated subjects, T790 testing is not required.

d) Measurable disease according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1)

   i) Target lesions may be located in a previously irradiated field if there is documented (radiographic) disease progression in that site after the completion of radiation therapy.

e) No prior systemic therapy for advanced or metastatic NSCLC, except for one or two prior lines of first- or second-generation EGFR TKI and/or osimertinib. Prior adjuvant or neoadjuvant chemotherapy for early stage lung cancer is permitted as long as all toxicities have resolved or stabilized.

   i) Prior EGFR TKI therapy must have been completed at least 2 weeks prior to first dose of study treatment

   ii) Switch between first- or second-generation EGFR TKI due to toxicity with no evidence of disease progression is acceptable and will not be considered as multiple lines of EGFR therapy. Switch treatment to osimertinib is also allowed. Further questions regarding eligibility of subjects with TKI treatment should be directed to the Medical Monitor.

   iii) Prior treatment with the combination of an EGFR TKI and a VEGF inhibitors (eg, bevacizumab, ramucirumab) is allowed.

f) Subjects must have sample available for PD-L1 IHC testing by the central lab. For subjects who were treated with first- or second- generation TKI, T790M testing using tissue sample will be performed by a central or local laboratory during the screening period. For subjects who were treated with osimertinib, T790M testing is not required.

i) Either a formalin-fixed, paraffin-embedded (FFPE) tissue block or unstained tumor tissue sections, with an associated pathology report, must be submitted [redacted] prior to randomization. The tumor tissue sample may be fresh or archival prior to enrollment, and there has been no systemic therapy given after the sample was obtained (except prior 1L or 2L EGFR TKIs).The archival tissue is preferred to be obtained within 6 months before the study treatment. If the archival tissue was obtained > 6 months before the study treatment, the approval of Medical Monitor is required.

ii) Tissue must be a core needle biopsy, excisional, or incisional biopsy. Fine needle biopsies or drainage of pleural effusions with cytospins are not considered adequate for [redacted] review and randomization. Biopsies of bone lesions that do not have a soft tissue component or decalcified bone tumor samples are also not acceptable

g) Subjects are eligible if CNS metastases are considered to be adequately controlled and/or treated before or during the screening period 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 randomization. In addition, subjects must be either off corticosteroids, or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent) for at least 2 weeks prior to randomization. Subjects with asymptomatic CNS metastasis are eligible.

Exclusion:

a) Subjects with known EGFR mutation, T790M positive who failed the 1L first- or second-generation generation TKI should receive osimertinib first as the SOC. These subjects are only eligible if they fail osimertinib as 2L.

b) Subjects with known ALK translocations which are sensitive to available targeted inhibitor therapy are excluded. If tested, use of an FDA-approved test is strongly encouraged. Subjects with unknown or indeterminate ALK status may be enrolled.

c) As of Amendment 02, the criterion regarding CNS metastases was moved to the Inclusion Criteria.

d) Subjects with carcinomatous meningitis

e) As of Amendment 1, the criterion excluding known cMET amplification is no longer applicable.

f) Subjects with known SCLC transformation

g) Subjects who have progressed within 3 months of the first dose of 1L or 2L EGFR TKI.

Study Drug: includes both Investigational [Medicinal] Products (IP/IMP) and Non-investigational [Medicinal] Products (Non-IP/Non-IMP) as listed:

Study Drug for CA209722		
Medication	**Potency**	**IP/Non-IP**
Nivolumab Solution for Injection	100 mg (10 mg/mL)	IP
Ipilimumab Solution for Injection	200 mg (5mg/mL)	IP
Carboplatin Solution for Injection	450 mg/vial (10 mg/mL)	IP
Carboplatin Injection (China)	Varies per market product	IP
Cisplatin Concentrate for Solution for Infusion	100 mg/vial (1 mg/mL)	IP
Cisplatin Infusion (China)	Varies per market product	IP

Study Drug for CA209722		
Medication	**Potency**	**IP/Non-IP**
Pemetrexed Powder for Concentrate for Solution for Infusion	500 mg/vial	IP
Pemetrexed Disodium for Injection (China)	500 mg/vial	IP

NOTE: As per revised protocol 04, Arm B has closed enrollment.

Study Assessments:

Efficacy

Radiographic tumor response will be assessed starting at Week 7 (± 7 days), then every 6 weeks (± 7 days) until Week 49 and every 12 weeks (± 7 days) thereafter, until disease progression is documented treatment is discontinued (whichever occurs later), or the start of subsequent anti-cancer therapy. Subjects with brain metastasis may have surveillance MRI (preferred) or CT with contrast approximately every 12 weeks from the date of first dose, or sooner if clinically indicated.

Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible. Change in tumor measurements and tumor response will be assessed by the BICR using the RECIST 1.1 criteria.

Safety

Subjects will be evaluated for safety if they have received any study drug. Toxicity assessments will be continuous during the treatment phase. Once subjects reach the survival follow-up phase, either in person or documented telephone calls to assess the subject's status are acceptable. Adverse events and laboratory values will be graded according to the NCI-CTCAE version 4.

Outcomes Research Assessments

The EQ-5D-3L will be collected in order to assess the impact of study treatment on generic health-related quality of life, which will also be used in populating health economic models most notably, a cost effectiveness analysis. The Lung Cancer Symptom Scale (LCSS) will be collected to assess the impact of study treatment on patient reported disease-related symptoms.

Statistical Considerations:

Sample Size:

The study accounts for primary endpoint PFS assessed by BICR comparison between nivolumab plus pemetrexed/platinum (Arm A) vs pemetrexed plus platinum (Arm C). No interim analysis for PFS is planned. A two-month delayed separation in PFS was assumed, with a pemetrexed plus platinum arm median PFS of 4.5 months and a nivolumab plus pemetrexed/platinum arm with median PFS of 6.5 months. Approximately 233 PFS events observed among the 270 randomized subjects (135 per Arms A and C), provide an average 83% power to detect a HR of 0.692 with type 1 error of 0.05.

Previously (before revised protocol 04), subjects were randomized among 3 arms in a 1:1:1 ratio.

Revised protocol 04 withholds randomization into Arm B of nivolumab plus ipilimumab but continues randomizing eligible subjects into either nivolumab plus platinum doublet chemotherapy arm (Arm A) or platinum doublet chemotherapy arm (Arm C) in 1:1 ratio. Approximately 270 subjects will be randomized between Arms A and C.

The PFS analysis will be conducted when the following conditions have been met: 233 PFS events have been reported and/or minimum follow up is at least 6 months. After analysis of PFS by BICR, OS will be tested in a hierarchical fashion.

Endpoints: PFS assessment by BICR is the primary endpoint for this study. PFS is defined as the time between the date of randomization and the first date of documented progression, as determined by BICR, or death, whichever occurs first. Subjects who die without a reported 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 their date of randomization. Subjects who started non-study anti-cancer therapy without a prior reported progression will be censored on the date of their last evaluable tumor assessment or prior to the initiation of subsequent anti-cancer therapy.

- OS is the key secondary endpoint: OS is defined as the time between the date of randomization and the date of death. OS will be censored on the last date a subject was known to be alive.
- ORR per RECIST 1.1 by BICR is a secondary endpoint. The ORR is defined as the number of subjects with a best objective response (BOR) of complete response (CR) or partial response (PR) divided by the number of randomized subjects for each treatment group. The BOR is defined as the best response designation, as determined by BICR, recorded between the date of randomization and the date of objectively documented progression per RECIST 1.1 or the date of subsequent anti-cancer therapy, whichever occurs first. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR assessment.
- The other secondary endpoints include duration of response (DOR) by BICR and the 9-month and 12-month PFS rates by BICR. DOR is defined as the time between the date of first confirmed response to the date of the first documented tumor progression (per RECIST 1.1) by BICR or death. Subjects who neither progress nor die will be censored on the date of their last assessment.

Exploratory Endpoints:

- Safety and tolerability objective will be measured by the incidence of adverse events, serious adverse events, death, and laboratory abnormalities
- PFS, OS, and ORR by PD-L1 status (≥ 1% and < 1%/not evaluable/indeterminate) (source: clinical database)

[redacted]

- To assess health-related quality of life using the EQ-5D-3L and LCSS
- To evaluate ORR, PFS and OS in the subjects treated with nivolumab plus ipilimumab (Arm B)
- To evaluate PFS after next line of treatment (PFS2) of nivolumab plus pemetrexed/platinum vs. pemetrexed plus platinum in EGFR mutation positive, metastatic or recurrent NSCLC

[redacted]

Analyses: Analysis of PFS will be conducted first followed by analysis of OS in hierarchical order. Primary PFS analysis will be conducted using a 2-sided log-rank test stratified by PD-L1 status, by presence or absence of brain metastases, smoking history (current/former smokers or never smokers) and prior use of osimertinib in randomized subjects to compare Arm A to Arm C. HR and corresponding 2-sided 95% CI will be estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by the above stratification factors. PFS curves, PFS medians with 95% CIs, and PFS rates at 6, 9 and 12 months with 95% CIs will be estimated using Kaplan-Meier methodology.

The key secondary endpoint of OS will be tested if PFS superiority is demonstrated for Arm A versus Arm C. The OS hypothesis testing will be conducted using a 2-sided log-rank test stratified by PD-L1 status, by presence or absence of brain metastases, smoking history, and by prior use of osimertinib in all randomized subjects to compare Arm A to Arm C. HR and corresponding 2-sided 95% CI will be estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by the stratification factors. OS curves, OS medians with 95% CIs, and OS rates at 9, 12, and 24 months with 95% CIs will be estimated using Kaplan-Meier methodology.

ORR analysis will be conducted at the time for PFS analysis. An estimate of the difference in ORRs and corresponding 95% CI will be calculated using Cochran-Mantel-Haenszel (CMH) methodology and stratified by PD-L1 status, by presence or absence of brain metastases, smoking status, and by prior use of osimertinib to compare Arm A to Arm C. Additionally, ORRs and their corresponding 95% exact CIs will be calculated using the Clopper-Pearson method for each arm.

PFS, OS, and ORR will be analyzed within each PD-L1 status subgroup (≥ 1% and < 1%/not evaluable/indeterminate (source: clinical database) by applying unstratified model. These analyses by PD-L1 status will be descriptive and not adjusted for multiplicity.

Descriptive analyses for PFS, OS and ORR will be provided for Arm B.

Safety analyses will be performed in all treated subjects. Descriptive statistics of safety will be presented using NCI CTCAE version 4. All on-study AEs, drug-related, AEs, SAEs and drug-related SAEs will be tabulated using worst grade per NCI CTCAE v4 criteria by system organ class and MedDRA preferred term. On study lab parameters including hematology, chemistry, liver function, thyroid function, and renal function will be summarized using worst grade per NCI CTCAE v4 criteria.

LCSS and EQ-5D-3L questionnaire complete rates, defined as the proportion of questionnaires actually received out of the expected number (ie, the number of subjects still on treatment in follow-up), will be calculated and summarized at each assessment point (each on-treatment assessment and assessments at Follow-up Visits 1 and 2).

The rate of disease-related symptom improvement as measured by the LCSS average symptom burden index (ASBI) at 12 and 24 weeks after the first dose (at Weeks 13 and 25 assessments) and its corresponding 95% exact CIs will also be calculated by Clopper-Pearson method for each randomized arms (all randomized patients). In a similar fashion, the rate of disease-related symptoms stability (no improvement or worsening) and rate of symptom worsening at 12 and 24 weeks after the first dose (at Weeks 13 and 25 assessments) will be calculated. For the each of these time periods (Weeks 13 and 25), an odds ratio across study arms (and its 95% CI) of the proportion of patients at each level (improvement, stability, worsening) will be calculated, with Arm A being compared to Arm C. In addition, the time to first symptom deterioration (TTSD) as measured by the ASBI of the LCSS will be evaluated, with the TTSD in Arm A to be compared to Arm C. The LCSS ASBI score and its change from baseline will be summarized using descriptive statistics (N, mean, median, SD, and 95% CI) at each assessment point by treatment group as randomized.

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1 INTRODUCTION AND STUDY RATIONALE

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related mortality worldwide, accounting for approximately 18% of all cancer deaths.[1] Despite treatment with platinum-based chemotherapy, the standard of care for first-line therapy, subjects with metastatic NSCLC have a median survival of approximately 10 months, and a 5-year survival rate of less than 5%.[2] Approximately 85% of lung cancer is NSCLC, and of these, approximately 80% are non-squamous, and 20% are squamous histology. The use of platinum-based chemotherapy doublets, given for up to 6 cycles, is standard of care for subjects with newly diagnosed advanced or metastatic NSCLC who do not have epidermal growth factor receptor (EGFR) mutation or ALK translocation.

The identification of EGFR-sensitizing mutations in a subset of subjects with lung adenocarcinoma has transformed the management of NSCLC. Approximately 15% of Western subjects and up to 60% of Asian subjects with NSCLC adenocarcinomas have tumors driven by an EGFR mutation.[3] Among the newer treatments available for the treatment of NSCLC are targeted therapies including erlotinib, gefitinib and afatinib. In a multicenter, open-label trial, subjects with metastatic NSCLC whose tumors had EGFR mutations received either erlotinib 150 mg/day orally (n = 86) or doublet chemotherapy (n=88).[4] Subjects were stratified by EGFR mutation and Eastern Cooperative Oncology Group Performance Status (ECOG PS) (PS 0 vs PS 1 vs PS 2). The trial endpoints included progression-free survival (PFS) (primary), overall survival (OS), and objective response rate (ORR) (secondary). A median PFS of 10.4 months was observed in the erlotinib arm versus 5.2 months in the platinum-based chemotherapy arm (hazard ratio [HR] 0.34 [95% confidence interval [CI]: 0.23, 0.49], P < 0.001). Median OS was 22.9 months and 19.5 months in the erlotinib and chemotherapy arms, respectively (HR 0.93 [95% CI: 0.64, 1.35], P = 0.6482). Subjects on the erlotinib arm had an ORR of 65% while those on the chemotherapy arm had an ORR of 16%.

Despite an impressive ORR and PFS, most subjects develop progression of disease on tyrosine kinase inhibitor (TKI) therapy after a median of 10-16 months.[5] In approximately 50% of cases, progression is attributable to the secondary mutation, T790M in exon 20 of EGFR.[6] In 2015, the FDA approved AZD9291, a third-generation irreversible EGFR TKI for treatment of subjects with EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy. In T790M-positive, AZD9291 achieved an ORR of 64%; however, similar benefit was not observed in the T790M negative population where the ORR was only 22%.[7] Therapeutic options for T790M negative subjects are limited, with chemotherapy remaining as the standard of care. Although limited data exists in this population, subgroup analysis suggests that these subjects achieve clinical benefit to chemotherapy comparable to those observed in the EGFR wild-type population. In the IMPRESS study, subjects were randomized 1:1 to either gefitinib 250 mg once daily or placebo and cisplatin 75 mg/m^2 and pemtrexed 500 mg/mg^2. The median PFS was 5.4 months in both groups (95% CI in the geftinib group, 4.5, 5.7; in the placebo group 4.6, 5.5). The objective response rate 32% in the gefitinib group and 34% in the placebo group (odds ratio, 0.92, 95% CI 0.55, 1.55).[8]

Immunotherapeutic approaches recently have demonstrated clinical efficacy in several cancer types, including melanoma, head and neck squamous cell, hormone-refractory prostate cancer, renal cell carcinoma (RCC), and squamous and non-squamous NSCLC.[9] Tumors may modulate and evade the host immune response through a number of mechanisms, including down regulation of tumor-specific antigen expression and presentation, secretion of anti-inflammatory cytokines, and upregulation of inhibitory ligands. T cell checkpoint regulators such as CTLA-4 and programmed death-1 (PD-1, CD279) are cell surface molecules that, when engaged by their cognate ligands, induce signaling cascades down-regulating T cell activation and proliferation.

One proposed model by which therapeutic T cell checkpoint inhibitors derive antitumor activity is through breaking of immune tolerance to tumor cell antigens.

Nivolumab (BMS-936558) is a fully human, IgG4 (kappa) isotype mAb that binds PD-1 on activated immune cells and disrupts engagement of the receptor with its ligands PD-L1 (B7 H1/CD274) and PD-L2 (B7-DC/CD273), thereby abrogating inhibitory signals and augmenting the host antitumor response. In early clinical trials, nivolumab has demonstrated activity in several tumor types, including melanoma, RCC, and NSCLC.[10]

Nivolumab is now approved in the United States and Europe to treat metastatic NSCLC in subjects with progression on or after platinum-based chemotherapy and who have progressed after EGFR TKI. Nivolumab is also approved for metastatic melanoma, previously-treated classical Hodgkin lymphoma, previously-treated squamous cell carcinoma of head and neck, previously-treated advanced RCC, and previously-treated locally advanced or metastatic urothelial carcinoma. Nivolumab is also approved in Japan for treatment of subjects with unresectable melanoma, advanced or recurrent NSCLC, and previously-treated locally advanced or metastatic urothelial carcinoma.[11]

The approval in squamous NSCLC was based on the results of CA209017, a randomized trial of nivolumab versus docetaxel. The median OS for subjects in the nivolumab arm was 9.2 months versus 6 months for those in the docetaxel arm (HR = 0.59). Improvement in survival was observed for nivolumab regardless of PD-L1 expression, though there was a trend toward better efficacy for those with PD-L1 expressing tumors.[12] A single arm trial (CA209063) of 117 subjects with metastatic squamous NSCLC with progression after platinum-based chemotherapy and at least 1 additional systemic regimen showed a 15% ORR, of whom 59% had response durations of 6 months or longer.[13]

The approval in non-squamous NSCLC is based on a second Phase 3 study, CA209057, which met its primary endpoint of superior OS of nivolumab versus docetaxel in subjects with previously treated non-squamous NSCLC at a preplanned interim analysis.[14] Subjects in the nivolumab arm had a 27% reduction in risk of death (HR = 0.73; P = 0.0015). Interaction p values, reported for PD-L1 expression subgroups by each of the predefined expression levels (1%, 5%, and 10%), suggested a clinically important signal of a predictive association. Nivolumab also significantly improved ORR vs docetaxel (P=0.0246), with ORR as high as 36% in subjects with PD-L1 expressing tumors. OS approximately doubled with nivolumab vs docetaxel across the PD-L1

expression continuum. In contrast, no statistically significant difference in OS was seen between nivolumab and docetaxel when PD L1 was not expressed in the tumor, although PD-L1 non-expressers also experience durable responses. Subjects with known EGFR mutation that progressed after prior TKI therapy and chemotherapy were eligible for this trial. Single agent activity of nivolumab appears to be less active in patients with known EGFR mutations (HR = 1.18, 95% CI: 0.69, 2.00).

In general, nivolumab is well tolerated, with a favorable safety profile relative to anticipated toxicities based on an immunostimulatory mechanism of action.

Combining immunotherapeutic agents with different mechanisms of action offers the possibility of a synergistic response.

PD-1 and CTLA-4 are both co-inhibitory molecules, but evidence suggests that they use distinct mechanisms to limit T cell activation. Preliminary indirect data from peripheral T cell assessments suggest that a given T-cell checkpoint inhibitor may modulate host immune cell phenotype rendering them more susceptible to alternate checkpoint inhibitors and thereby enhancing anti-tumor activity.

The safety and efficacy was investigated in a Phase 3 clinical trial in patients with advanced melanoma. Significant improvements were seen in median PFS, investigator-assessed ORR, and change in tumor burden in those subjects receiving the nivolumab and ipilimumab combination compared to nivolumab monotherapy or ipilimumab monotherapy. Although the data suggests an increase in adverse event frequency of nivolumab and ipilimumab combination regimen as seen in ipilimumab monotherapy or nivolumab monotherapy, there were no unexpected AEs noted in the combination regimen of nivolumab and ipilimumab.[15] The FDA approved the combination of nivolumab and ipilimumab for the treatment of BRAF V600 wild type or V600 mutation positive unresectable or metastatic melanoma in January of 2016.

In study CA209012, the combination of nivolumab plus ipilimumab is being evaluated at several different doses and schedules. While the schedule evaluated in melanoma was not found to be tolerable in NSCLC, the study identified alternative schedules with an acceptable tolerability profile and encouraging activity with response rates greater than 39%. PFS and OS are encouraging in the nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 week (Q6) or every 12 week (Q12) week cohorts. Subjects with known EGFR mutation who have received prior EGFR TKI were eligible to participate. Similar clinical activity was observed regardless of EGFR mutation. A confirmed ORR of 50% was observed in the 8 subjects with known EGFR mutation (who were on different dosing schedules). The median PFS was 13.6 months, and OS was not reached at the time of the analysis.

Nivolumab added to chemotherapy has been evaluated in several cohorts of chemotherapy-naive subjects with advanced NSCLC in study CA209012. Nivolumab 10 mg/kg was combined with gemcitabine and cisplatin and pemetrexed and cisplatin. Nivolumab 10 mg/kg and 5 mg/kg was combined with paclitaxel and carboplatin.[16]

The safety profile of nivolumab plus platinum-doublet chemotherapy reflects additive toxicities of the individual agents, which were manageable using established safety guidelines. No dose-limiting toxicities were observed during first 6 weeks of treatment. The observed response rates of nivolumab and chemotherapy were similar to that of platinum-doublet chemotherapy alone, though the duration of responses is longer. The median duration of response across all the nivolumab and chemotherapy cohorts was 27.3 weeks. The 1-year survival rate for all cohorts combined is 71%.

Study CA209012 also evaluated the safety, tolerability, and clinical activity of nivolumab combined with erlotinib (20 TKI pretreated, 1 TKI naïve).[17] The erlotinib-naïve subject achieved a near complete response (CR) at the time of data analysis (duration 72.3+weeks; ongoing). Three erlotinib-pretreated subjects achieved a PR. Responses were seen in subjects who had previously received multiple lines of EGFR inhibitor therapy and regardless of T790M mutation. Responses were ongoing in 3 subjects at the time of analysis. PFS rate at 24 weeks was 51% while median PFS was 29.4 weeks. The 1-year OS rate was 73% (median OS not reached).

As of revised protocol 04, CA209722 is an open-label, randomized Phase 3 trial of nivolumab plus pemetrexed/platinum versus pemetrexed/platinum in EGFR mutation positive NSCLC whose tumor has progressed on 1L or 2L EGFR TKI.

The central questions of the study will be to determine if concurrent administration of nivolumab plus pemetrexed/platinum improves PFS compared to pemetrexed/platinum in EGFR mutation positive NSCLC whose tumor has progressed on 1L or 2L EGFR TKI.

1.1 Study Rationale

1.1.1 Rationale of Combining Nivolumab with Chemotherapy (Arm A)

The interaction of a tumor with the immune system is complex. Tumors and the tumor microenvironment are known to express a variety of factors that impede a robust immune response from eliminating the tumor. Soluble and membrane-bound factors have been shown to inhibit the cytolytic activity of tumor infiltrating T-cells (eg, PD-L1 expression; TGF-beta). In addition, some tumor-derived factors are able to enhance the immune system counter-regulatory systems (eg, increased T-regulatory cells). Finally, suboptimal tumor antigen delivery and presentation has been postulated as another mechanism by which tumors can successfully evade immune system recognition.

Cancer therapeutics such as chemotherapy may modulate tumor/immune-system interactions in favor of the immune system. Chemotherapy can result in tumor cell death with a resultant increase in tumor antigen delivery to antigen-presenting cells. Tumor cell death may also lead to a reduction in soluble and membrane-bound factors inhibiting tumor-infiltrating T-cells. Chemotherapy may also disrupt immune system regulatory networks by decreasing numbers of T-regulatory cells.

Nivolumab added to chemotherapy has been evaluated in several cohorts of chemotherapy-naive subjects with advanced NSCLC in study CA209012. Nivolumab 10 mg/kg was combined with gemcitabine and cisplatin and pemetrexed + cisplatin. Nivolumab 10 mg/kg and 5 mg/kg was combined with paclitaxel and carboplatin.[16]

The safety profile of nivolumab plus platinum-doublet chemotherapy reflects additive toxicities of the individual agents, which were manageable using established safety guidelines. No dose-limiting toxicities were observed during first 6 weeks of treatment. The frequency of most immune-related select AEs was higher for the combination than what has been observed for nivolumab monotherapy. However, these treatment-related AEs, including pneumonitis, were effectively managed and did not lead to any deaths. Pneumonitis of any grade was reported in 7 subjects (13%): Grade 3-4 in 4 subjects (7%). Twelve (21%) subjects discontinued due to treatment-related AEs (Table 1.1.1-1).

The observed response rates of nivolumab and chemotherapy were similar to that of platinum-doublet chemotherapy alone, though the duration of response is longer. In the 15 subjects that received nivolumab 10 mg/kg plus pemetrexed and cisplatin, 47% achieved a PR or CR. The median duration of response was 24.4 weeks with a 1-year survival rate of 87% (Table 1.1.1-2). Published data suggest that clinical benefit to chemotherapy alone is similar in EGFR mutation positive and wild-type patients. Although the clinical activity of nivolumab and chemotherapy in EGFR mutation positive patients has not been established, the addition of nivolumab to chemotherapy may prolong the durability of response translating in a survival benefit.

Activity was evaluated by PD-L1 expression and was observed in subjects with both PD-L1 expressing and non-expressing tumors. Overall, 79% (44/56) of subjects had evaluable tumor samples. At the ≥ 1% expression level, the response rate was 48% and 43% for expressers and non-expressers, respectively. The 1-year OS was 70% and 76% for expressers and non-expressers, respectively.

Table 1.1.1-1: Safety in CA209012

	Total (N=56)		
	All Grades	**Grade 3**	**Grade 4**
Subjects with any treatment-related AE, % (n)	95 (53)	41 (23)	4 (2)[a]
Treatment-related AE in >15% of Patients, % (n)			
Fatigue	71(40)	5 (3)	0
Nausea	46 (26)	2 (1)	0
Decrease Appetite	36 (20)	2 (1)	0
Alopecia	30 (17)	0	0
Anemia	27 (15)	4 (2)	0
Rash	27 (15)	2 (1)	0
Arthralgia	21 (12)	0	0
Diarrhea	21 (12)	2 (1)	0
Constipation	20 (11)	0	0
Peripheral Neuropathy	20 (11)	0	0

[a] Grade 4 events: neutrophil count decreased (n = 1), pneumonitis and neutropenia (n = 1 each; occurred in the same patient).

Table 1.1.1-2: Efficacy of First-Line Treatment of Nivolumab/Chemotherapy Combination in CA209012

Efficacy of First-Line Treatment of Nivolumab/Chemotherapy Combination in CA209012				
	Nivolumab 10 mg/kg			Nivolumab 5 mg/kg
	Gem/Cis (n=12)	Pem/Cis (n=15)	Pac/Carb (n=15)	Pac/Carb (n=14)
ORR, %	33	47	47	43
SD, %	58	47	27	43
Median Duration of Response, Weeks	45	24.4	27.3	27.3
12-mo OS rate, %	50	87	72	86
18-mo OS Rate, %	33	60	40	62
Median OS, Weeks	51	83	65	Not Reached

1.1.2 Rationale for Combination of Nivolumab and Ipilimumab (Arm B):

NOTE: As per revised protocol 04, Arm B has closed enrollment.

Combining immunotherapeutic agents with different mechanisms of action offers the possibility of synergistic response. PD-1 and CTLA-4 are both co-inhibitory molecules, but evidence suggests that they use distinct mechanisms to limit T-cell activation. Preliminary indirect data from peripheral T-cell assessments suggests that a given T-cell checkpoint inhibitor may modulate host immune cell phenotype rendering them more susceptible to alternate checkpoint inhibitors and thereby enhancing anti-tumor activity.

Preclinical data indicate that the combination of PD-1 and CTLA-4 receptor blockade may improve antitumor activity. In vitro combinations of nivolumab plus ipilimumab increase IFN-γ production 2- to 7-fold over either agent alone in a mixed lymphocyte reaction. Increased antitumor activity of the combination was also observed in 3 of 5 syngeneic murine cancer models. In a murine melanoma vaccine model, blockade with either CTLA-4 or PD-1 antibodies increased the proportion of CTLA-4 and PD-1-expressing CD4/CD8 tumor infiltrating T effector cells, and dual blockade increased tumor infiltration of T effector cells and decreased intratumoral T regulatory cells, as compared to either agent alone.[18]

The combination of nivolumab and ipilimumab was evaluated in CA209004 (MDX1106-04), a Phase 1b, multiple ascending dose study in subjects with treatment-naive and previously-treated advanced melanoma. Results showed promising activity with higher but tolerable toxicity than ipilimumab alone. Based on these data, CA209069, a Phase 2 study, compared the combination to

ipilimumab alone in treatment-naïve subjects with advanced melanoma: nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks for 4 doses followed by nivolumab 3 mg/kg every 2 weeks versus ipilimumab 3 mg/kg every 3 weeks for 4 doses.[19] In subjects with BRAF wild type tumors, the ORR was 61% (44/72), including 22% (16/72) CRs in the group treated with the combination, compared to 11% (4/37) with 0 CRs in those treated with ipilimumab alone. The median PFS was not reached in the combination versus 4.4 months for ipilimumab alone (HR = 0.4). Recently, a Phase 3 study (CA209067, n = 945) reported significantly improved PFS and ORR with the combination of nivolumab and ipilimumab versus ipilimumab alone in previously untreated melanoma. The median PFS was 6.9 months (95% confidence interval [CI], 4.3 to 9.5) in the nivolumab group, 11.5 months (95% CI, 8.9 to 16.7) in the nivolumab plus ipilimumab group, and 2.9 months (95% CI, 2.8 to 3.4) in the ipilimumab group. Significantly longer PFS was observed in the nivolumab plus ipilimumab group than in the ipilimumab group (hazard ratio for death or disease progression, 0.42; 99.5% CI, 0.31 to 0.57; $P < 0.001$) and in the nivolumab group than in the ipilimumab group (hazard ratio, 0.57; 99.5% CI, 0.43 to 0.76; $P < 0.001$). The hazard ratio for the comparison between the nivolumab plus ipilimumab group and the nivolumab group was 0.74 (95% CI, 0.60 to 0.92).

In addition, deep and durable responses were observed in previously treated, extensive stage small cell lung cancer (SCLC), with a response rate of 31.1% with the combination of nivolumab and ipilimumab.[20]

Based on the initial data in melanoma and the activity observed with nivolumab and ipilimumab in lung cancer, the nivolumab plus ipilimumab combination has been also evaluated as first-line therapy in subjects with advanced NSCLC. In CA209012, early combination cohorts evaluated 2 dosing schedules that were studied in the CA209004 study in melanoma[21]:

- Nivolumab 1 mg/kg + ipilimumab 3 mg/kg, every 3 weeks for 4 doses, followed by nivolumab 3 mg/kg q 2 weeks (Arms G and H, n=24);
- Nivolumab 3 mg/kg + ipilimumab 1 mg/kg, every 3 weeks for 4 doses, followed by nivolumab 3 mg/kg q 2 weeks (Arms I and J, n=25)

These regimens resulted in significant toxicity, with 39% of subjects discontinuing treatment due to a treatment-related adverse event. Thus, additional combination cohorts were initiated (Arms N, O, P, Q), using lower doses of both nivolumab and ipilimumab, or the approved dose of nivolumab with less frequent dosing of ipilimumab. These new regimens were much better tolerated, and the safety data are not dissimilar to what has been observed in the nivolumab monotherapy cohort (Arm F in CA209012) (Table 1.1.2-1).

Table 1.1.2-1: Treatment-related Adverse Events from Selected Cohorts in CA209012						
Arm[a]	**No. Subjects/ arm**	**Follow-up time (median, wks)**	**No. Subjects still on treatment**	**No. Subjects with drug-related AEs**	**No. Subjects with grade 3-4 drug-related AEs**	**No. subjects d/c due to drug-related AEs (all grades)**
N[b]	31	72	6 (19%)	24 (77%)	9 (29%)	4 (13%)
O[b]	40	27	14 (35%)	29 (73%)	14 (35%)	3 (8%)
P[b]	38	37	20 (53%)	28 (74%)	11 (29%)	2 (5%)
Q[b]	39	34	15 (39%)	27 (69%)	11 (28%)	4 (10%)
F[c]	52	62	5 (10%)	37 (71%)	10 (19%)	5 (10%)

[a] N:nivolumab 1 mg/kg plus ipilimumab 1 mg/kg every 3 weeks x 4, followed by nivolumab 3 mg/kg every 2 weeks; O: nivolumab 1 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks; P: nivolumab 3 mg/kg every 2 weeks plus ipilimumab every 12 weeks; Q: nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks; F: nivolumab 3 mg/kg every 2 weeks

[b] based on August 2015 database lock

[c] based on March 2015 database lock

Activity was observed in all cohorts, with response rates greater than 39% in the 2 cohorts in which nivolumab was dosed at 3 mg/kg (N3). PFS and OS is also encouraging in the nivolumab 3 mg/kg cohorts (Table 1.1.2-2).

Subjects with known EGFR mutation who have received prior EGFR TKI were eligible to participate. Similar clinical activity was observed regardless of EGFR mutation. A confirmed ORR of 50% was observed in the 8 subjects with known EGFR mutation. The median PFS was 13.6 months, and OS was not reached at the time of the analysis. Of note, 7 out of the 8 subjects had tumors that expressed the PD-L1 protein and 3 of the 4 responders had a known history of smoking (Table 1.1.2-3).[22]

Clinical activity was observed in subjects with and without PD-L1 expressing tumors, though there was a greater magnitude of efficacy in subjects with PD-L1 expressing tumors. In subjects with PD-L1 expressing tumors (≥ 1 % level), the response rate was 57% with nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 6 or 12 weeks. For subjects with PD-L1 non-expressing tumors, the response rates were lower, but the subject numbers are small. For subjects with PD-L1 expressing and non-expressing tumors, the nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks is being further explored in a Phase 3 study in first-line NSCLC (CA209227). This dosing schedule will also be used in the experimental arm of the CA209722 study.

Table 1.1.2-2: Efficacy of First-Line Treatment of Nivolumab/Ipilimumab Combination in CA209012

	Nivo 1 mg/kg + Ipi 1 mg/kg Q3W (n=31)	Nivo 1 mg/kg + Ipi 1 mg/kg Q6W (n=40)	Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q12W (n=38)	Nivo 3 mg/kg Q2W+ Ipi 1 mg/kg Q6W (n=39)
Confirmed ORR, % (95% CI)	**13 (4, 30)**	**25 (13, 41)**	**39 (24, 57)**	**31 (17, 48)**
PFS rate at 24 wks (95% CI)	55 (36, 73)	58 (41, 73)	74 (57, 87)	51 (35, 68)
mPFS, mos (95% CI)	10.6 (2.1, 16.3)	4.9 (2.8,)	8.0 (4.2,)	8.3 (2.6,)
Median length of follow-up, months	16.6	6.2	8.4	7.7

CI, confidence interval; mPFS, median progression-free survival; PFS, progression-free survival; ORR, objective response rate

Table 1.1.2-3: Efficacy by PD-L1 Expression

	Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q12W	Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q6W	Nivolumab 3 mg/kg Q2W
ORR, % (n/N)			
< 1% PD-L1	30 (3/10)	0 (0/7)	14 (2/14)
≥ 1% PD-L1	57 (12/21)	57 (13/23)	28 (9/32)
≥ 50% PD-L1	100 (6/6)	86 (6/7)	50 (6/12)
Median PFS (95% CI), mo			
< 1% PD-L1	4.7 (0.9, NR)	2.4 (1.7, 2.9)	6.6 (2.0, 11.2)
≥ 1% PD-L1	8.1 (5.6, NR)	10.6 (3.6, NR)	3.5 (2.2, 6.6)
≥ 50% PD-L1	13.6 (6.4, NR)	NR (7.8, NR)	8.4 (2.2 (NR)
1-year OS rate (95% CI), %			
< 1% PD-L1	NC	NC	79 (47, 93)
≥ 1% PD-L1	90 (66, 97)	83 (60, 93)	69 (50, 82)
≥ 50% PD-L1	NC	100 (100, 100)	83 (48, 96)

NC, not calculated (when > 25% of patients are censored); NR, not reached due to high percentage of ongoing response.
Combination data based on a February 2016 database lock; monotherapy data based on a March 2015 database lock except for IS data, which are based on an August 2015 database lock.

1.1.3 Rationale for Removing Combination of Nivolumab and Ipilimumab Arm

The understanding of immuno-oncology has continued evolving as data emerges from both clinical studies and basic research. A recent meta-analysis of several clinical studies in advanced NSCLC patients with EGFR mutations in second line of therapy suggested a trend toward less clinical benefit from PD-(L)1 monotherapy when compared with chemotherapy (pooled HR, 1.11; 95%CI: 0.80, 1.53).[23] New body of evidence is also accumulating to show that Tumor Mutational Burden (TMB) in EGFR-mutated NSCLC patients is significantly lower than that in EFGR wild-type NSCLC patients.[24] The newly released data from CheckMate 227 indicated that NSCLC patients with low TMB are unlikely to derive PFS or ORR benefit from nivolumab and ipilimumab combination therapy when compared with chemotherapy[25], suggesting that the combination of nivolumab and ipilimumab has a lower chance of success compared to chemotherapy-containing arms. Thus, using nivolumab plus ipilimumab as one of the study arms has become potentially sub-optimal for this patient population moving forward. No safety concerns were identified in the nivolumab and ipilimumab combination arms based on periodical DMC safety review.

1.1.4 Rationale for Adding Subjects Previously Treated with Osimertinib

The treatment landscape of EGFR-mutated NSCLC has evolved rapidly with the newly released data on osimertinib. Osimertinib has been the standard of care as a 2L treatment for the patients who failed the 1L first- and/or second-generation TKIs with T790M mutation. It has recently been approved as a 1L treatment for EGFR-mutated NSCLC regardless of T790M status in US[26], Europe[27], and Japan, and is expected to be approved in other countries in the near future. Patients that receive osimertinib as 1L therapy will therefore be included in the study in addition to patients that still receive first- or second-generation TKIs as 1L. Patients that failed osimertinib as 2L therapy will also be included in the study. Patients that fail 1L or 2L osimertinib represent a high unmet need due to the lack of treatment options since resistance mechanisms have not be identified yet.

1.1.5 Stratification by PD-L1 Expression, Smoking History, Brain Metastasis, and Osimertinib Use

The impact of PD-L1 expression on the clinical activity of nivolumab plus ipilimumab or nivolumab plus chemotherapy in subjects with known EGFR mutation is unclear. In the nivolumab plus chemotherapy cohorts of study CA209012, activity was evaluated by PD-L1 expression and was observed in subjects with both PD-L1 expressing and non-expressing tumors. Overall, 79% (44/56) of subjects had evaluable tumor samples. At the ≥1% expression level, the response rate was 48% and 43% for expressers and non-expressers, respectively. The 1-year overall survival was 70% and 76% for expressers and non-expressers, respectively. A small number of subjects with EGFR mutation were enrolled in these cohorts; therefore, the impact of PD-L1 expression in this population was not assessed.

Subjects with known EGFR mutation who have received prior EGFR TKI were eligible to participate in the nivolumab plus ipilimumab cohorts of study CA209012. Similar clinical activity was observed regardless of EGFR mutation. A confirmed ORR of 50% was observed in the 8

subjects with known EGFR mutation. The median PFS was 13.6 months, and OS was not reached at the time of analysis. Of note, 7 out of the 8 subjects had tumors that expressed the PD-L1 protein and 3 out of 4 responders had a known history of smoking. The clinical benefit of nivolumab plus ipilimumab in EGFR mutation patients who are PD-L1 non-expressers is unclear at this time. In addition, limited data exist on the impact of smoking history and the efficacy profile of nivolumab in patients with EGFR mutation.

In order to better understand the impact of PD-L1 expression, smoking history, and brain metastasis on clinical response to nivolumab plus ipilimumab or nivolumab plus platinum chemotherapy in subjects with EGFR mutation, study CA209722 will stratify by PD-L1 expression in tumor cells (≥1% or < 1%/not evaluable/indeterminate), smoking history (current/former smokers or never smokers), and brain metastasis (present or absent).

Revised protocol 04 expands the patient population to include subjects who failed osimertinib. There is little data on the clinical benefit of immunotherapy on the patients who failed the first- or second-generation TKIs versus those who failed osimertinib. To better understand the impact of prior treatment with osimertinib on the clinical benefit of nivolumab plus platinum chemotherapy in the NSCLC subjects with EGFR mutation, prior osimertinib treatment (yes vs no) and brain metastasis will be added as a stratification factor.

1.1.6 Rationale for Nivolumab 360 mg Flat Dose

Nivolumab monotherapy has been extensively studied in NSCLC patient population in studies CA209003, CA209063, CA209017, and CA209057 with body weight normalized dosing (mg/kg). Nivolumab pharmacokinetics (PK) and exposures of subjects in these studies have been characterized by population pharmacokinetic (PPK) analysis of data collected from these studies, together with PK data from several Phase 1, 2, and 3 clinical studies of nivolumab monotherapy in solid tumors. Nivolumab PK was determined to be linear, with dose proportional exposures over a dose range of 0.1 to 10 mg/kg. Nivolumab clearance and volume of distribution was found to increase with increasing body weight, but the increase was less than proportional, indicating that a mg/kg dose represents an over-adjustment for the effect of body weight on nivolumab PK.

Flat dosing offers several advantages over body weight normalized dosing, including reduced potential for dosing errors and shortened dosage preparation time. A flat dose of 360 mg every 3 weeks is expected to produce the equivalent average exposure to 3 mg/kg every 2 weeks at the median body weight of ~80 kg in nivolumab-treated subjects.

A PPK model predicted overall nivolumab exposures across subjects with a wide range of body weight (35-160 kg) for a 360 mg every 3 weeks flat dose to be similar to that from 3 mg/kg every 2 weeks. Although the flat dose is expected to lead to higher exposure in lighter patients, relative to the exposure in heavier patients given the relationship between nivolumab PK and body weight, the predicted median and 95th percentile of exposures from these regimens are maintained well below those in 10 mg/kg every 2 weeks, which was established as a safe and well-tolerable dose.

In addition, data from the Japanese Phase 1 study ONO-4538-01 did not demonstrate dose-limiting toxicity at nivolumab up to 20 mg/kg every 2 weeks in Japanese subjects and showed similarity in

PK properties between Global and Japanese population. Therefore, the proposed 360 mg flat dose is expected to be safe and tolerable in an Asian population.

Nivolumab 5 or 10 mg/kg every 3 weeks plus platinum-based chemotherapy was evaluated in CA209012 and deemed to be tolerable. In addition, nivolumab 360 mg every 3 weeks plus platinum-based chemotherapy is further being evaluated in the global randomized Phase 3 trial (CA209227).

1.1.7 Rationale for 24 Month Duration of Treatment

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 or nivolumab combined to ipilimumab indicates that most of the responses generally occurring early, with a median time to response of 2 to 4 months including in patients with NSCLC.[12,14,28] A recent analysis in a melanoma study suggests the majority of patients who discontinue nivolumab and/or ipilimumab for toxicity maintain disease control in the absence of further treatment.[29] Furthermore, a limited duration of ipilimumab including only 4 induction doses resulted in long-term survival in patients with metastatic melanoma, with a sustained plateau in survival starting at around year 3.[30] In the Phase I dose escalation cohort expansion trial, CA209003, 129 patients with heavily pretreated advanced NSCLC received nivolumab at 1, 3, or 10 mg/kg IV once every 2 weeks in 8-week cycles for up to 96 weeks. Among the 22 patients (17%) with objective responses, the estimated median response duration was 17.0 months. In the 18 responders who discontinued nivolumab therapy for reasons other than disease progression (completion of maximum cycles, n=7; adverse events, n=8; withdrawal of consent, n =2; other, n=1), 9 patients (50%) maintained a response for more than 9 months after the end of therapy (range, 9.2 to 16.4 months).[31]

For these reasons, in study CA209722, treatment with nivolumab or nivolumab with ipilimumab will be given for up to 24 months (96 weeks) in the absence of disease progression or unacceptable toxicity. Chemotherapy will be given as per the study dosing schedule including pemetrexed maintenance until progression or unacceptable toxicity. Treatment with nivolumab with or without ipilimumab can be reinitiated as per the initial schedule for subsequent disease progression and administered for up to 1 additional year (prior to revised protocol 06).

1.1.8 Rationale for Shorter Infusion Times for Nivolumab and Ipilimumab

Long infusion times, especially when multiple agents are administered sequentially to an individual, place a burden on patients and treatment centers. Establishing that nivolumab and ipilimumab can be safely administered using shorter infusion times of 30-minute duration for nivolumab and ipilimumab in subjects will diminish the burden, provided there is no change in safety profile.

Previous clinical studies of nivolumab monotherapy and ipilimumab monotherapy and the combination of nivolumab and ipilimumab have used a 60-minute infusion duration for nivolumab and 90-minute infusion duration for ipilimumab (1 to 3 mg/kg dosing for both). However, both

nivolumab and ipilimumab have been administered at up to 10 mg/kg with the same infusion duration.

Nivolumab has been administered safely over 60 minutes at doses ranging up to 10 mg/kg safely over long treatment duration. In Study CA209010 (a Phase 2, randomized, double-blinded, dose-ranging study of nivolumab in subjects with advanced/metastatic clear cell RCC), a dose association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg and 18.5% at 10 mg/kg). All the events were Grade 1-2 and were manageable. An infusion duration of 30 minutes for 3 mg/kg nivolumab (30% of the dose provided at 10 mg/kg) or nivolumab 360 mg are not expected to present any safety concerns compared to the prior experience at 10 mg/kg nivolumab dose infused over a 60 minute duration.

Similarly, ipilimumab at 10 mg/kg has been safely administered over 90 minutes. In the CA184022 study, where ipilimumab was administered up to a dose of 10 mg/kg, on-study drug-related hypersensitivity events (Grade 1-2) were reported in 1 (1.4%) subject in the 0.3 mg/kg and in 2 (2.8%) subjects in the 10 mg/kg group. There were no drug-related hypersensitivity events reported in the 3 mg/kg group. Across the 3 treatment groups, no Grade 3-4 drug-related hypersensitivity events were reported, and there were no reports of infusion reactions. Ipilimumab 10 mg/kg monotherapy has also been safely administered as 90-minute infusion in large Phase 3 studies in prostate cancer (CA184043) and as adjuvant therapy for stage 3 melanoma (CA184029), with infusion reactions occurring in subjects. Administering 1 mg/kg of ipilimumab represents one-tenth of the 10 mg/kg dose.

Of note, CA209153, a Phase 3b/4 safety study of nivolumab in subjects with metastatic NSCLC who have progressed during or after at least 1 prior systemic regimen used a 30-minute infusion in a cohort of subjects with no safety issues.

Overall, infusion reactions including high-grade hypersensitivity reactions have been uncommon across nivolumab or ipilimumab clinical studies or the combination of nivolumab and ipilimumab. Furthermore, a 30-minute break after the first infusion for combination cohort will ensure the appropriate safety monitoring before the start of the second infusion. Overall, a change in safety profile is not anticipated with 30-minute infusion of nivolumab, ipilimumab, or combination.

1.1.9 Rationale for Platinum Doublet Chemotherapy as Comparator

In 2015, the FDA approved AZD9291, a third-generation irreversible EGFR TKI for treatment of subjects with EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy. In T790M-positive, AZD9291 achieved an ORR of 64%; however, similar benefit was not observed in the T790M negative population where the ORR was only 22%.[6] Therapeutic options for T790M negative subjects are limited with platinum-based chemotherapy remaining as the standard of care. In addition, randomized data in this population is limited. However, the expected clinical benefit to platinum-based chemotherapy is similar to those observed in EGFR wild-type population. In the randomized, Phase 3 IMPRESS study, subjects with advanced NSCLC with acquired resistance to EGFR TKI were randomized to gefitinib plus pemetrexed/platinum vs pemetrexed/platinum. The ORR was 34% and median PFS was 5.4 months (95% CI 4.6, 5.5).[8] The pemetrexed/platinum combination is a well-accepted

standard of care in subjects with non-squamous histology NSCLC. In a Phase 3 study comparing cisplatin/gemcitabine with pemetrexed/cisplatin in chemotherapy-naive patients with advanced stage NSCLC, pemetrexed/cisplatin improved PFS and OS compared to gemcitabine/cisplatin in subjects with non-squamous NSCLC. Due to its well established safety and efficacy profile, pemetrexed/platinum was selected as the control arm for study CA209722.

1.1.10 Rationale for Open-Label Design

This study will use an open-label design. Due to the obvious difference in chemotherapy and immunotherapy-related toxicities, the different schedules and durations of therapy in the treatment arms, different dose modification rules for safety management, including different dose delay rules per arm, and different premedication requirements according to chemotherapy, an open-label design is appropriate. An open-label design will also help ensure that immune-related toxicities in subjects receiving immunotherapy are promptly identified and managed.

Because this study will be open-label, a blinded independent central review (BICR) will be used to review tumor images in all randomized subjects to determine all response-related endpoints.

1.1.11 Rationale for Permitting Continued Treatment in Select Cases of Progressive Disease

Accumulating clinical evidence indicates some subjects treated with immune system stimulating agents may develop progression of disease (by conventional response criteria) before demonstrating clinical objective responses and/or stable disease. This phenomenon was observed in approximately 10% of subjects in the Phase 1 study of nivolumab and also with ipilimumab monotherapy.[32] Two hypotheses have been put forth to explain this phenomenon. First, enhanced inflammation within tumors could lead to an increase in tumor size which would appear as enlarged index lesions and as newly visible small non-index lesions. Over time, both the malignant and inflammatory portions of the mass may then decrease leading to overt signs of clinical improvement. Alternatively, in some individuals, the kinetics of tumor growth may initially outpace anti-tumor immune activity. With sufficient time, the anti-tumor activity will dominate and become clinically apparent. Therefore, for Arms A and B, subjects will be allowed to continue study therapy after initial investigator-assessed RECIST 1.1-defined progression if they are assessed to be deriving clinical benefit and tolerating study drug (Section 4.5.8). Such subjects must discontinue study therapy upon evidence of further progression.

1.1.12 Rational for Revised Sample Size

CA209722 study faced enrollment challenges due to low disease prevalence in some geographic locations, tissue sample requirements following the first-line therapy, and evolving standard of care treatments for the NSCLC population with EGFR mutation. Despite the efforts to boost the enrollment through protocol amendments, participation lagged. Furthermore, the COVID-19 pandemic significantly affected recruitment and enrollment globally by limiting the ability to reach the previously planned sample size in a timely manner. Accordingly, enrollment in this study was stopped in June, 2020.

At study concept, PFS data following immunotherapy plus chemotherapy in this population were not available for robust statistical assumptions to assess the study objectives. However, currently available external data from IMpower150, a study of atezolizumab (anti-PD-L1 agent) plus chemotherapy (n = 34) compared with chemotherapy (n = 45), showed a greater than 3-month statistically significant and clinically meaningful improvement in PFS endpoint as the second line treatment in EGFR mutated NSCLC.[33] Given the limited sample size of IMpower150, it is reasonable to predict that the addition of nivolumab to SOC chemotherapy may provide clinically meaningful improvement of 2 months in PFS. Therefore, the statistical assumption in this study was revised to 2-months improvement in PFS with delay in separation of curves. With the revised assumptions, sample size of approximately 135 subjects per arm (Arm A and Arm C) will provide 83% power to detect an average HR of 0.692 with a significance level of 0.05.

It is well accepted that overall survival of the NSCLC patients with EGFR mutation is impacted by the complexity of the subsequent lines of therapies as salvage therapies and the heterogeneity of the resistance mechanisms of first-line TKIs. Therefore, the revised sample size is calculated using the PFS endpoint only, while it was previously calculated using the OS endpoint as well.

1.2 Research Hypothesis

In NSCLC subjects with EGFR mutation (ie, G719X, L861Q, Del 19, and L858R) whose tumor has progressed on first-line (1L) or second-line (2L) EGFR TKI, concurrent administration of nivolumab plus pemetrexed/platinum has superior efficacy defined by PFS to pemetrexed/platinum alone.

1.3 Objectives(s)

1.3.1 Primary Objectives

- To compare the PFS by BICR of nivolumab plus pemetrexed/platinum to pemetrexed plus platinum in EGFR mutation positive (ie, G719X, L861Q, Del 19, and L858R), metastatic or recurrent NSCLC that has progressed on 1L or 2L EGFR TKI

1.3.2 Secondary Objectives

- To compare the OS of nivolumab plus pemetrexed/platinum to pemetrexed plus platinum in EGFR mutation positive (ie, G719X, L861Q, Del 19, and L858R), metastatic or recurrent NSCLC whose tumors have progressed on 1L or 2L EGFR TKI
- To determine the ORR per RECIST 1.1 by BICR, the duration of response (DOR) by BICR, and the 9-month and 12-month PFS rates by BICR of nivolumab plus pemetrexed/ compared to pemetrexed plus platinum in EGFR mutation positive (ie, G719X, L861Q, Del 19, and L858R), metastatic or recurrent NSCLC that has progressed on 1L or 2L EGFR TKI

1.3.3 Exploratory Objectives:

- To assess the PFS by BICR, ORR (per RECIST 1.1) by BICR, DOR by BICR, and OS by PD-L1 status (≥ 1%, < 1%/not evaluable/indeterminate membranous staining in tumor cells)

in subjects treated with nivolumab plus pemetrexed/platinum compared to pemetrexed plus platinum

- To assess the safety and tolerability of nivolumab plus pemetrexed/platinum compared to pemetrexed plus platinum in EGFR mutation positive (ie, G719X, L861Q, Del 19, L858R), metastatic or recurrent NSCLC that has progressed on 1L or 2L EGFR TKI

[redacted]

- To assess health-related quality of life using the EQ-5D-3L and LCSS
- To evaluate ORR by BICR, DOR by BICR, PFS by BICR and OS of nivolumab plus ipilimumab in EGFR mutation positive (ie, G719X, L861Q, Del 19, and L858R), T790M negative, metastatic or recurrent NSCLC that has progressed on 1L EGFR TKI
- To evaluate PFS after next line of therapy (PFS2) of nivolumab plus pemetrexed/platinum vs pemetrexed plus platinum in EGFR mutation positive (ie, G719X, L861Q, Del 19, L858R), metastatic or recurrent NSCLC

1.4 Product Development Background

Nivolumab is in clinical development for the treatment of subjects with NSCLC, RCC, melanoma, and other tumors (eg, glioblastoma multiforme, Hodgkin lymphoma, SCLC). Opdivo® is approved in the United States, European Union, and other countries for the treatment of patients with unresectable or metastatic melanoma, advanced NSCLC with progression on or after platinum-based chemotherapy, advanced RCC whose disease progressed on an antiangiogenic therapy (US and Japan), classical Hodgkin lymphoma that has relapsed or progressed after autologous hematopoietic stem cell transplantation and post-transplantation brentuximab vedotin treatment (US and Japan), pre-treated head and neck (US and Japan), and previously-treated locally advanced or metastatic urothelial carcinoma (US only). Approval in advanced NSCLC was based on 2 Phase 3 trials (CheckMate 017 and CheckMate 057) which demonstrated survival benefit over docetaxel across histologies. This study, CA209722, will evaluate the efficacy and safety of nivolumab plus pemetrexed/platinum and nivolumab in combination with ipilimumab in EGFR mutation, T790M negative NSCLC that has progressed after 1L EGFR TKI.

1.4.1 Mechanism of Action of Nivolumab

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses.[34,35,36] Support for the role of immunosurveillance in NSCLC is suggested in retrospective analyses

demonstrating a correlation between tumor infiltrating lymphocytes in surgically resected specimens and recurrence free survival.[37,38,39] Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor (TCR) 33, collectively, these signals govern the balance between T-cell activation and tolerance to antigens. PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA-4, ICOS, and BTLA.[28] PD-1 signaling has been shown to inhibit CD-28-mediated upregulation of IL-2, IL-10, IL-13, interferon-γ (IFN-γ) and Bcl-xL. PD-1 expression also been noted to inhibit T cell activation, and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes.[40] These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

In vitro, nivolumab binds to PD-1 with high affinity (EC50 0.39-2.62 nM) and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (IC50 ±1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4 and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction (MLR). Using a CMV re-stimulation assay with human peripheral blood mononuclear cells, the effect of nivolumab on antigen specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV specific memory T cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and result in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[41]

1.4.2 Clinical Pharmacology Summary

Single dose pharmacokinetics (PK) of nivolumab was evaluated in subjects with multiple tumor types in CA209001, whereas multiple dose PK is being evaluated in subjects in CA209003. In addition, a preliminary population pharmacokinetic (PPK) model has been developed with data from 350 subjects from CA209001, CA209002, and CA209003.

Single dose PK of nivolumab was evaluated in 39 subjects with multiple tumor types in study CA209001 in the dose range of 0.3 to 10 mg/kg. The median Tmax across single doses ranged from 1.6 to 3 hours with individual values ranging from 0.9 to 7 hours. Geometric mean Cmax and AUC(INF) of nivolumab administered at dosages of 0.3 mg/kg, 1 mg/kg, 3 mg/kg, and 10 mg/kg demonstrated approximate dose proportionality. Geometric mean clearance (CL), after a single intravenous (IV) dose, ranged from 0.13 to 0.19 mL/h/kg, while mean volume of distribution during the terminal phase (Vz) varied between 83 to 113 mL/kg across doses. There was moderate variability in PK parameters among subjects, with coefficient of variation (CV) of 20% to 32% in Cmax, 39% to 47% in AUC(INF), 17% to 43% in clearance, and 23% to 40% in Vz. The mean

terminal elimination half-life of nivolumab is 17 to 25 days, which is consistent with half-life of endogenous IgG4, indicating that the elimination mechanism of nivolumab may be similar to IgG4. Both elimination and distribution of nivolumab appear to be independent of dose in the dose range studied. Additional details are provided in the investigator brochure.

A preliminary PPK model was developed by nonlinear mixed effect modeling using data from 350 subjects from CA209001, CA209002 and CA209003. Clearance (CL) of nivolumab is independent of dose in the dose range (0.1 to 10 mg/kg) and tumor types studied. The body weight normalized dosing produces approximately constant trough concentrations over a wide range of body weights, and hence is appropriate for future clinical trials of nivolumab.

1.4.3 Mechanism of Action of Ipilimumab

CTLA-4, an activation-induced T-cell surface molecule, is a member of the CD28:B7 immunoglobulin superfamily that competes with CD28 for B7. CTLA-4 mediated signals are inhibitory and turn off T cell-dependent immune responses.[42,43] Ipilimumab is a fully human monoclonal IgG1κ that binds to the CTLA-4 antigen expressed on a subset of T cells from human and nonhuman primates. The proposed mechanism of action for ipilimumab is interference of the interaction of CTLA-4 with B7 molecules on APCs, with subsequent blockade of the inhibitory modulation of T-cell activation promoted by the CTLA 4/B7 interaction.

The safety profile of nivolumab and nivolumab plus ipilimumab is characterized by immune related toxicities, such as diarrhea, rash, pneumonitis, liver toxicity, and endocrinopathies. The frequencies and intensities of these events in the combination are variable and depend on the specific doses and schedule used. In the dosing schedules selected, these events were mostly low grade and manageable with the use of corticosteroids. Nivolumab and ipilimumab combination therapy has shown improved efficacy over either agent alone in melanoma.

1.4.4 Treatment of EGFR Mutation, T790M NSCLC whose Tumor Progressed on 1L EGFR TKI

The identification of EGFR-sensitizing mutations in a subset of subjects with lung adenocarcinoma has transformed the management of NSCLC. Despite impressive ORR and PFS with 1L EGFR TKI therapy, most subjects develop progression of disease on TKI therapy after a median of 10-16 months. In approximately 50% of cases, progression is attributable to the secondary mutation, T790M in exon 20 of EGFR. In 2015, the FDA approved AZD9291, a third-generation irreversible EGFR TKI for treatment of subjects with EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy. In T790M-positive, AZD9291 achieved an ORR of 64%; however, similar benefit was not observed in the T790M-negative population where the ORR was only 22%. Subjects with EGFR mutation, T790M-negative NSCLC who failed 1L EGFR TKI represent a great unmet need. Therapeutic options for T790M negative subjects are limited with platinum-based chemotherapy remaining as the standard of care. The expected clinical benefit to platinum-based chemotherapy is similar to those observed in EGFR wild-type population. In the randomized, Phase 3 IMPRESS study, subjects with advanced NSCLC with acquired resistance to EGFR TKI were randomized to gefitinib plus pemetrexed/platinum vs pemetrexed/platinum. The ORR was 34% with a median

PFS of 5.4 months (95% CI 4.6-5.5).[8] The pemetrexed/platinum combination is a well-accepted standard of care in subjects with non-squamous histology NSCLC. In a Phase 3 study comparing cisplatin/gemcitabine with pemetrexed/cisplatin in chemotherapy-naive patients with advanced stage NSCLC, pemetrexed/cisplatin improved PFS and OS compared to gemcitabine/cisplatin in subjects with non-squamous NSCLC.[44] In the PARAMOUNT study, pemetrexed was demonstrated to improve PFS and OS, when continued as maintenance therapy in patients with non-squamous NSCLC who did not progress after completion of induction treatment with pemetrexed/cisplatin.[45] However, there have been no substantial improvements in long-term survival, making NSCLC a persistent area of high unmet medical need.

The major adverse events related to platinum doublet chemotherapy regimens are primarily hematologic. With pemetrexed/cisplatin, the rate of Grade 3/4 neutropenia is 15%, the rate of Grade 3/4 anemia is 6% and the rate of Grade 3/4 thrombocytopenia is 4%.

1.4.4.1 Cisplatin

Cisplatin is a platinum-based drug that is used in NSCLC. Cisplatin is administered intravenously at a dose of 75 mg/m² over 120 minutes or per institutional standard after pemetrexed. Subjects who are receiving cisplatin must be monitored for nephrotoxicity, ototoxicity and neuropathy in addition to myelosuppression. Caution must be observed in cases of nausea, vomiting, and dehydration. Dose modifications according to toxicities are noted in Section 4.5.5. For additional information regarding risks, as well as preparation and storage information, please consult the local prescribing information for cisplatin.

1.4.4.2 Carboplatin

Carboplatin is a platinum-based drug that is used in combination with a taxane, gemcitabine, or pemetrexed for treatment of NSCLC. Carboplatin is administered intravenously at a dose of AUC 5 or 6 mg/mL/min (per Calvert formula) over 30 minutes or per institutional standard after the use of pemetrexed.[46] Subjects who are receiving carboplatin must be monitored for myelosuppression and anaphylaxis. Dose modifications according to toxicities are noted in Section 4.5.5. For preparation and storage, please consult the prescribing information for carboplatin.

1.4.4.3 Pemetrexed

Pemetrexed is a folate analog metabolic inhibitor indicated as initial treatment for locally advanced or metastatic non-squamous NSCLC in combination with cisplatin or carboplatin. Pemetrexed is also indicated as maintenance treatment for locally advanced or metastatic non-squamous NSCLC subjects whose disease has not progressed after platinum-based first-line chemotherapy. Pemetrexed is administered intravenously at a dose of 500 mg/m² on Day 1 of each 21-day cycle. Cisplatin should be administered 30 minutes after pemetrexed at a dose of 75 mg/m². Carboplatin should be administered 30 minutes after pemetrexed at AUC of 5 or 6.

The premedication regimen for pemetrexed includes folic acid and vitamin B12 as well as dexamethasone or equivalent to reduce cutaneous reactions. Subjects receiving pemetrexed should be monitored prior to each dose using CBC and renal function tests. If marrow suppression is noted, dose modifications are noted in Section 4.5.5. For renal toxicity, pemetrexed should be held

when the creatinine clearance (CrCl) < 45 mL/minute. Caution should be used among subjects who are receiving non-steroidal anti-inflammatory drugs (NSAIDs) and who have mild to moderate renal insufficiency (CrCl between 50 and 79 mL/minute). Caution should also be used when nephrotoxic drugs are administered with pemetrexed. For additional information regarding premedication regimen, risks, preparation, and storage information, please consult the local prescribing information for pemetrexed.

1.5 Overall Risk/Benefit Assessment

Subjects with EGFR mutation, T790M negative NSCLC who failed 1L or 2L EGFR TKI represent a great unmet need. In T790M-positive, AZD9291 achieved an ORR of 64%; however, similar benefit was not observed in the T790M negative population where the ORR was only 22%. Therapeutic options for T790M negative subjects are limited with platinum-based chemotherapy remaining as the standard of care with an expected PFS of 5-6 months and mOS of 10-12 months. The clinical activity of nivolumab observed to date in NSCLC, including 2 positive Phase 3 studies demonstrating prolonged survival with nivolumab monotherapy compared to docetaxel in squamous and non-squamous NSCLC after platinum failure, suggests the potential for improved clinical outcomes. CA209057 (non-squamous NSCLC) study demonstrated OS was superior for subjects receiving nivolumab compared to those receiving docetaxel.

The potential benefit of nivolumab plus ipilimumab or nivolumab plus platinum-doublet chemotherapy over standard of care platinum-based therapy in EGFR mutation, T790M negative NSCLC is not yet known as well as for those who relapse after osimertinib where T790M is not relevant to tumor growth.

The CA209722 revised protocol 04 reflects the current treatment landscape in patients with EGFR-mutated metastatic NSCLC. The enrollment to nivolumab and ipilimumab combination arm (ie, Arm B) has stopped as emerging data suggest that the immunotherapy alone has a lower chance of success compared to chemotherapy containing therapies and becomes potentially sub-optimal treatment option for patients who failed 1L or 2L TKI. With recent approval of osimertinib in the first-line setting and limited treatment option post osimertinib, the revised protocol allows the enrollment of patients who failed osimertinib. Patients that fail osimertinib represent a high unmet need.

In CA209057 study, interaction P values reported for PD-L1 expression subgroups by each of the pre-defined expression levels suggested a clinically important signal of a predictive association. Based on these data, CA209722 will stratify subjects based on PD-L1 status. Additional stratification factors include presence or absence of brain metastases at randomization, smoking history (current/former or never smoker), and prior osimertinib use.

The platinum-based chemotherapy regimens have well described safety profiles, characterized by myelosuppression and other regimen-specific non-hematologic toxicities, such as peripheral neuropathy, nausea/vomiting, and renal impairment. The safety profile of nivolumab plus platinum-doublet chemotherapy reflects additive toxicities of the individual agents. The frequency of most immune-related, select AEs was higher with nivolumab plus platinum-doublet chemotherapy in CA209-012 compared to those previously reported with nivolumab

monotherapy. However, these treatment-related AEs, including pneumonitis, were effectively managed with established guidelines and did not lead to any deaths.

The safety profile of nivolumab and nivolumab plus ipilimumab is characterized by immune-related toxicities, such as diarrhea, rash, pneumonitis, liver toxicity, and endocrinopathies.[21] The frequencies and intensities of these events in the combination are variable and depend on the specific doses and schedule used. In the dosing schedules selected for this trial, these events were mostly low grade and manageable with the use of corticosteroids. No safety concerns were identified in patients who received nivolumab and ipilimumab combination treatment in CA209722 study based on periodical DMC safety review.

In order to assess the potential benefit of nivolumab plus pemetrexed/platinum or nivolumab plus ipilimumab compared to standard of care pemetrexed/platinum in subjects with EGFR mutation, T790M negative NSCLC whose tumor progress on 1L EGFR TKI, a randomized trial will be performed. Subjects will be randomized to 1 of 3 arms: nivolumab plus pemetrexed/platinum, nivolumab plus ipilimumab, or pemetrexed/platinum.

Revised protocol 04 will focus on assessing the potential benefit of nivolumab plus pemetrexed/platinum compared to standard of care pemetrexed/platinum in NSCLC subjects with EGFR mutation whose tumor progress on 1L or 2L EGFR TKI. Subjects will be randomized in a 1:1 ratio to nivolumab plus pemetrexed/platinum arm or pemetrexed/platinum arm.

Revised protocol 05 updates the study title to align with the updated study design in revised protocol 04.

To assure an ongoing favorable risk/benefit assessment for subjects enrolled onto CA209722, an independent Data Monitoring Committee (DMC) will be utilized to monitor the safety and activity of the treatments throughout the conduct of the trial.

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) and applicable local requirements.

The study will be conducted in compliance with the protocol. The protocol and 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 Sponsor or designee 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, Sponsor or designee 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.

Sponsor or designee 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:

- 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.
- Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
- 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.
- 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.
- 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.
- 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, randomized, Phase 3 study in subjects with EGFR-mutated, metastatic or recurrent NSCLC whose tumors have progressed on a 1L first- or second-generation EGFR TKI and who are T790M negative or whose tumors have progressed on osimertinib.

In revised protocol 03, subjects were randomized to 3 arms in a 1:1:1 ratio. Subjects were stratified by PD-L1 expression (≥1% or <1%/not evaluable/indeterminate), by presence or absence of brain metastases, and by smoking history (current/former or never smoker).

Revised protocol 04 stopped enrollment in Arm B (nivolumab plus ipilimumab) but continued to randomize eligible subjects into either nivolumab plus platinum doublet chemotherapy arm (Arm A) or platinum doublet chemotherapy arm (Arm C) in a 1:1 ratio. Randomization to Arm A or Arm C will be stratified by PD-L1 expression (≥ 1% or < 1%/not evaluable/indeterminate), brain metastases (presence or absence), smoking history (current/former or never smoker), and prior osimertinib use (yes or no). Approximately 500 subjects were planned to be randomized to Arms A or C. Subjects already randomized in Arm B of nivolumab plus ipilimumab remained on treatment at the discretion of the investigator.

Revised protocol 05 updated the study title to align with the updated study design in revised protocol 04.

With the adjustment of PFS assumptions based on external data, the number of subjects randomized to Arm A and Arm C will be approximately 270 subjects. The total number of subjects randomized in the study is now expected to be approximately 350 subjects.

Consistent with updated treatment duration of nivolumab-containing regimens (at the program level), reference to treating subjects with disease progression or recurrence as continued treatment beyond 24 months is no longer offered. Reference to continued treatment and the associated guidelines have been deleted from Sec. 4.5.9.

PD-L1 expression will be assessed in tumor cells, using 1% as the expression level and categorized into 2 separate groups (≥ 1% or < 1%/not evaluable/indeterminate). PD-L1 status will be determined by immunohistochemical (IHC) staining of PD-L1 protein in the submitted tumor sample and categorized as follows:

- PD-L1 positive - defined as ≥ 1% tumor cell membrane staining positive in a minimum of 100 evaluable tumor cells
- PD-L1 negative – defined as < 1% tumor cell membrane staining positive in a minimum of 100 evaluable tumor cells
- PD-L1 not evaluable/indeterminate - defined as subjects with insufficient quantity of tumor biopsy specimens for IHC staining and analysis or subjects with tumors that are unable to determine the PD-L1 status, despite appropriate amount of tissue sample. For subjects with PD-L1 not evaluable/indeterminate tumors, key efficacy and safety parameters will be summarized and grouped with PD-L1 negative subjects. Enrollment in this stratum will be capped to 10% of subjects.

Screening begins by establishing the subject's initial eligibility and signing of the informed consent (ICF). Subjects must be randomized within 42 days after signing the informed consent unless otherwise noted. Tumor tissue (archival [preferably within 6 months before first dose of study drug] or fresh tumor biopsy) must be submitted to a third-party vendor for determination of PD-L1 status. For subjects who failed 1L first- or second-generation TKI, the T790M testing will be conducted using tumor tissue (either at local lab with an approved test or at central lab) and only subjects with T790M negative status will be randomized. For subjects who failed osimertinib, T790M testing is not required.

The subject is assessed for study eligibility as described in Table 5.1-1. All screening assessments and procedures (except for a fresh biopsy for PD-L1/T790M and brain MRI/CT scans following the treatment of current brain metastasis) must be performed within 28 days prior to randomization.

As of revised protocol 04, the Treatment Phase begins when the randomization call is made into the Interactive Web Response System (IWRS). The subject is randomly assigned to 1 of the 2 treatment arms: Arm A or Arm C. Enrollment to Arm B is closed. Study treatment must begin within 7 days of randomization.

<u>Arm A: Nivolumab plus Platinum-doublet Chemotherapy (Each Cycle = 21 days [3 weeks])</u>

- Nivolumab will be administered IV every 3 weeks with platinum-doublet chemotherapy (investigator's choice of cisplatin or carboplatin) IV for a maximum of 4 cycles.

  - Nivolumab 360 mg IV, followed by pemetrexed (500 mg/m^2) with cisplatin (75 mg/m^2) administered on Day 1 of each cycle
- OR
  - Nivolumab 360 mg IV, followed by pemetrexed (500 mg/m^2) with carboplatin (AUC 5 or 6) administered on Day 1 of each cycle

If a subject who is receiving nivolumab and pemetrexed experiences an adverse event and the investigator can attribute it to either nivolumab or pemetrexed, then that agent can be discontinued, and the other agent can be continued until disease progression or unacceptable toxicity.

Following completion of the fourth cycle of nivolumab/chemotherapy, all subjects who have not experienced disease progression should continue nivolumab 360 mg IV and pemetrexed (500 mg/m^2) every 3 weeks until the progression of disease, discontinuation due to toxicity, withdrawal of consent, or study closure, whichever comes first. Nivolumab should only be administered for a maximum of 24 months (96 weeks) from the first study treatment.

Treatment with nivolumab beyond initial investigator-assessed RECIST 1.1-defined progression is permitted if the subject has investigator-assessed clinical benefit and is tolerating treatment, as specified in Section 4.5.8.

Arm B: Nivolumab plus ipilimumab (Each Cycle = 14 day [2 weeks])

Arm B is closed as of revised protocol 04.

Nivolumab 3 mg/kg IV will be administered every 2 weeks and ipilimumab 1 mg/kg IV will be administered every 6 weeks until the progression of disease, discontinuation due to toxicity, withdrawal of consent, a maximum of 24 months (96 weeks) from the first study treatment, or study closure.

Treatment beyond initial investigator-assessed RECIST 1.1-defined progression is permitted if the subject has investigator-assessed clinical benefit and is tolerating treatment, as specified in Section 4.5.8.

Arm C: Platinum Doublet Chemotherapy (Each Cycle = 21 days [3 weeks])

Platinum-doublet chemotherapy (investigator's choice of cisplatin or carboplatin) is administered IV in 3-week cycles for up to a maximum of 4 cycles.

- Pemetrexed (500 mg/m^2) with cisplatin (75 mg/m^2) administered on Day 1 of each cycle
  OR
- Pemetrexed (500 mg/m^2) with carboplatin (AUC 5 or 6) administered on Day 1 of each cycle.

Platinum-doublet chemotherapy will continue until disease progression, unacceptable toxicity (Section 4.5.7.3), or completion of the 4 cycles, whichever comes first.

Subjects who have stable disease or response after 4 cycles of pemetrexed with cisplatin or carboplatin should continue pemetrexed alone as maintenance therapy until disease progression, or unacceptable toxicity.

All Arms

Subjects will be assessed for response by CT or MRI beginning at Week 7 (± 7 days), every 6 weeks (± 7 days) until Week 49, and then every 12 weeks (± 7 days) until progression. Tumor assessments must continue per protocol until RECIST 1.1 progression is confirmed by BICR. OS will be followed continuously while subjects are on the study drugs and every 3 months via in-person or phone contact after a subject discontinues the study drugs.

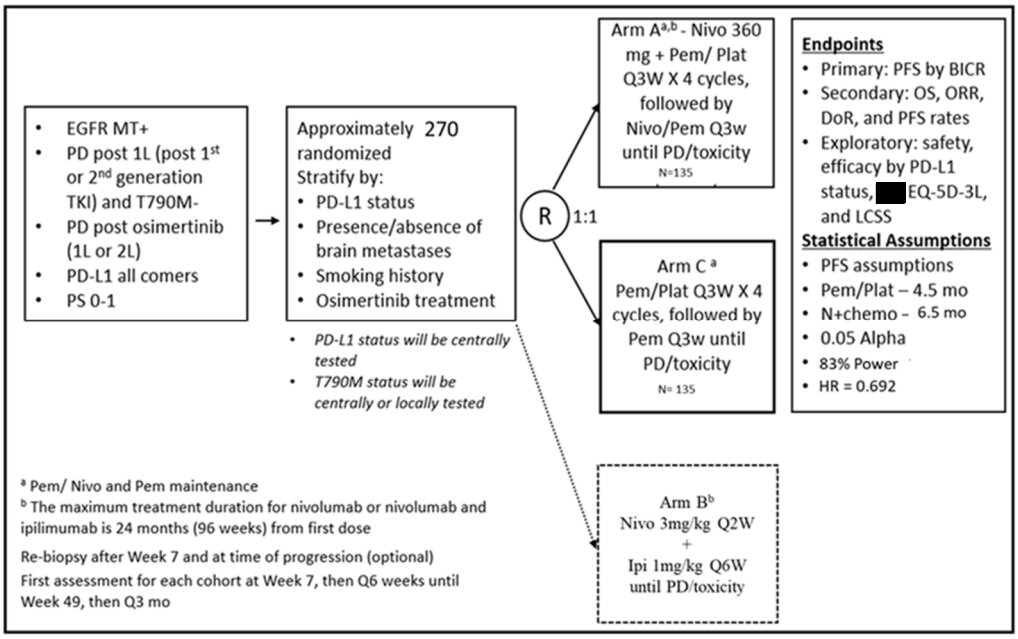
The Follow-Up Phase begins when the decision to discontinue a subject from all treatment, including maintenance therapy, is made, or the subject has reached the maximum treatment duration for nivolumab and ipilimumab.

Subjects who discontinue treatment for reasons other than disease progression will continue to have tumor assessments (if clinically feasible) according to the schedule in Table 5.1-2 until progression or the start of the subsequent anti-cancer therapies.

Subjects will be followed for drug-related toxicities until these toxicities resolve, return to baseline, or are deemed irreversible. All adverse events will be documented for a minimum of 100 days after the last dose of study medication.

After completion of the first 2 follow-up visits, subjects will be followed every 3 months for survival. Survival follow-up visits may be performed by phone contact or office visit (Section 3.6). BMS may request that survival data be collected on all randomized subjects outside of the protocol defined window. At the time of that request, each subject will be contacted to determine their survival status unless the subject had withdrawn consent for all contact.

Figure 3.1-1: Study Design Schematic



The start of the trial is defined as first patient first visit. End of trial is defined as last patient's last overall survival assessment. Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected, if this is not the same.

3.2 Post Study Access to Therapy

At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study drug up to 12 months after the approval of investigational product by the responsible health authority or until the investigational product becomes commercially available within the country, or the maximum treatment duration as specified in the protocol, whichever occurs sooner. Study drug will be provided via an extension of the study, a rollover study requiring approval by responsible health authorities 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

For entry into the study, the following criteria MUST be met.

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

a) 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.

b) Subjects must be willing and able to comply with scheduled visits, treatment schedule, and laboratory testing.

2. Target Population

a) Eastern Cooperative Group (ECOG) Performance Status 0-1

b) Subjects with histologically confirmed Stage IV or recurrent EGFR-mutated (ie, G719X, L861Q, Del 19, and L858R) NSCLC (per the 7th International Association for the Study of Lung Cancer classification)47 with disease progression on one or two prior lines of treatment with EGFR TKIs (allowed TKIs must be approved by the local health authority, including but not limited to erlotinib, gefitinib afatinib, dacomitinib and osimertinib).

c) No evidence of exon 20 T790M mutation obtained at progression on prior first- or second-generation EGFR TKI therapy. Initial testing of blood samples is allowed in local laboratories using assays approved by local Health Authority only to rule out T790M positive subjects. T790M negative status must be confirmed by a central or a local laboratory on tissue samples using the cobas® EGFR Mutation Test v2 (US-IVD) in patients failing first- or second-generation TKIs. In osimertinib treated subjects, T790 testing is not required.

d) Measurable disease according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1)
   i) Target lesions may be located in a previously irradiated field if there is documented (radiographic) disease progression in that site after the completion of radiation therapy.

e) No prior systemic therapy for advanced or metastatic NSCLC, except for one or two prior lines of first- or second-generation EGFR TKI and/or osimertinib. Prior adjuvant or neoadjuvant chemotherapy for early stage lung cancer is permitted as long as all toxicities have resolved or stabilized.
   i) Prior EGFR TKI therapy must have been completed at least 2 weeks prior to first dose of study treatment
   ii) Switch between first- or second-generation EGFR TKI due to toxicity with no evidence of disease progression is acceptable and will not be considered as multiple lines of EGFR therapy. Switch treatment to osimertinib is also allowed. Further questions regarding eligibility of subjects with TKI treatment should be directed to the Medical Monitor.
   iii) Prior treatment with the combination of an EGFR TKI and a VEGF inhibitors (eg, bevacizumab, ramucirumab) is allowed.

f) Subjects must have sample available for PD-L1 IHC testing by the central lab. For subjects who were treated with first- or second- generation TKI, T790M testing using tissue sample will be performed by a central or local laboratory during the screening period. For subjects who were treated with osimertinib, T790M testing is not required.
   i) Either a formalin-fixed, paraffin-embedded (FFPE) tissue block or unstained tumor tissue sections, with an associated pathology report, must be submitted for [redacted] prior to randomization. The tumor tissue sample may be fresh or archival prior to enrollment, and there has been no systemic therapy given after the sample was obtained (except prior 1L or 2L EGFR TKIs).The archival tissue is preferred to be obtained within 6 months before the study treatment. If the archival tissue was obtained ≥6 months before the study treatment, the approval of Medical Monitor is required.

ii) Tissue must be a core needle biopsy, excisional, or incisional biopsy. Fine needle biopsies or drainage of pleural effusions with cytospins are not considered adequate for [redacted] review and randomization. Biopsies of bone lesions that do not have a soft tissue component or decalcified bone tumor samples are also not acceptable

g) Prior palliative radiotherapy to non-CNS lesions must have been completed at least 2 weeks prior to randomization. Subjects with symptomatic tumor lesions at baseline that may require palliative radiotherapy within 4 weeks of randomization are strongly encouraged to receive palliative radiotherapy prior to randomization

h) Screening laboratory values must meet the following criteria (using CTCAE v4):
   i) WBC ≥ 2000/uL
   ii) Neutrophils ≥1500/uL
   iii) Platelet ≥ $100x10^3$/uL
   iv) Hemoglobin ≥ 9.0 g/dL
   v) Serum creatinine ≤ 1.5 x ULN and calculated creatinine clearance ≥ 50 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 1.0

   72 x serum creatinine in mg/ dL

   vi) AST ≤ 3.0 x ULN
   vii) ALT ≤ 3.0 x ULN
   viii) Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome who must have a total bilirubin level of < 3.0 x ULN)

i) Subject Re-enrollment: This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, subject has not been randomized / has not been treated) up to 2 times. If re-enrolled, the subject must be re-consented.

j) Subjects are eligible if CNS metastases are considered to be adequately controlled/treated before or during the screening period 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 randomization. In addition, subjects must be either off corticosteroids, or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent) for at least 2 weeks prior to randomization). Subjects with asymptomatic CNS metastasis are eligible.

k) Must have life expectancy of at least 3 months

3. Age and Reproductive Status

a) Males and Females, ≥18 years of age or age of majority

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) Women of childbearing potential (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 study drug plus 30 days (duration of ovulatory cycle) for a total of 5 months post-treatment completion (for subjects treated in Arms A and B)

e) WOCBP must also agree to follow instructions for method(s) of contraception from the time of enrollment for the duration of treatment with chemotherapy plus 5 half-lives of chemotherapy plus 30 days (duration of ovulatory cycle) for a total of 30 days post-treatment completion or a duration specified by the local labels of the chemotherapy drugs received, whichever is longer (for subjects treated in Arms A and C).
f) Males who are sexually active with 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 the study drug plus 90 days (duration of sperm turnover) for a total of 7 months post-treatment completion. In addition, male subjects must be willing to refrain from sperm donation during this time (for subjects treated in Arms A and B).
g) Males who are sexually active with WOCBP must agree to follow instructions for methods of contraception for the duration of treatment with chemotherapy plus 5 half-lives of chemotherapy plus 90 days (duration of sperm turnover) for a total of 90 days post-treatment completion of a duration specified by the local labels of the chemotherapy drugs received, whichever is longer (for subjects treated in Arms A and C).
h) Azoospermic males are exempt from contraceptive requirements. WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, and still must undergo pregnancy testing as described in this section.

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 on the use of highly effective methods of contraception (Appendix 1), which have a failure rate of < 1% when used consistently and correctly.

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Subjects with known EGFR mutation, T790M positive who failed 1L first- or second-generation TKI should receive osimertinib first as the SOC. These subjects are only eligible if they fail osimertinib as 2L.
b) Subjects with known ALK translocations which are sensitive to available targeted inhibitor therapy are excluded. If tested, use of an FDA-approved test is strongly encouraged. Subjects with unknown or indeterminate ALK status may be enrolled.
c) As of Amendment 02, this criterion has been moved to Inclusion Criterion 2j
d) Subjects with carcinomatous meningitis
e) As of Amendment 1, the criterion excluding known cMET amplification is no longer applicable.
f) Subjects with known SCLC transformation
g) Subjects who have progressed within 3 months of the first dose of 1L or 2L EGFR TKI.

2. Medical History and Concurrent Diseases

a) Subjects who have not recovered from the effects of major surgery or significant traumatic injury at least 14 days before randomization.

b) Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.

c) Other active malignancy requiring concurrent intervention.

d) Subjects with an active, known or suspected autoimmune disease. 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.

e) Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days prior to first dose of study treatment. Inhaled or topical steroids, and adrenal replacement steroid > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

f) Subjects with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity.

g) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at sites where mandated locally

h) Known medical condition that, in the investigator's opinion, would increase the risk associated with study participation or study drug administration or interfere with the interpretation of safety results

i) As of Amendment 03, this criterion has been moved to 3.c.

j) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways

k) Subjects who have received a live/attenuated vaccine within 30 days of first dose of study treatment

3. Physical and Laboratory Test Findings

a) Subjects with ≥ Grade 2 peripheral neuropathy

b) Subjects with active hepatitis B (positive hepatitis B surface antigen [HBsAg])

   i) Subjects must be willing and able to comply with scheduled visits, treatment schedule, and laboratory testing. Patients with past HBV infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBcAb] and absence of HBsAg) are eligible. HBV DNA must be obtained and confirm negative prior to randomization. HBV carriers or those patients requiring antiviral therapy are not eligible to participate.

   ii) Subject with active hepatitis C (positive hepatitis C virus [positive HCV RNA]). Patients positive for HCV antibody are eligible only if PCR is negative for HCV RNA.

c) HBV carriers or those subjects receiving antiviral treatment of hepatitis B virus or Hepatitis C are not eligible

4. Allergies and Adverse Drug Reaction

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

5. Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated. (Note: under certain specific circumstances a person who has been imprisoned may be included or permitted to continue as a subject. Strict conditions apply and Bristol-Myers Squibb approval is required).

b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

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.

3.3.3 Women of Childbearing Potential

Women 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 > 40 mIU/mL to confirm menopause.

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 judgement in checking serum FSH levels.

- 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. If the serum FSH level is > 40 mIU/mL at any time during the washout period, the woman can be considered postmenopausal.

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

The following medications are prohibited during the study (unless utilized to treat a drug related adverse event):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 3.4.3)
- Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of NSCLC)
- Antiviral treatment for HBV or HCV
- Caution should be applied in the administration of over-the-counter medications and herbal preparations during the conduct of the study. Consultation with Medical Monitor is encouraged.
- Any live/attenuated vaccines (eg, varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR], nasal flu vaccine, chicken pox [varicella]) should be avoided during the study treatment and until 100 days post last dose of study treatment

Investigators should refer to the local product labeling for the chemotherapy drugs selected for use in Arms A and C and for additional prohibited and restricted concomitant medications.

3.4.2 Other Restrictions and Precautions

Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization are excluded. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

It is the local imaging facility's responsibility to determine, based on subject attributes (eg, allergy history, diabetic history and renal status), the appropriate imaging modality and contrast regimen for each subject. Imaging contraindications and contrast risks should be considered in this assessment. Subjects with renal insufficiency should be assessed as to whether or not they should receive contrast and if so, what type and dose of contrast is appropriate. Specific to MRI, subjects with severe renal insufficiency (ie, estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73m^2) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this subject population. In addition, subjects are excluded from MRI if they have tattoos, metallic implants, pacemakers, etc. The ultimate decision to perform MRI in an individual subject in this study rests with the site radiologist, the investigator, and the standard set by the local Ethics Committee.

Caution should be used when administering NSAIDs concurrently with pemetrexed to patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min).

3.4.3 Permitted Therapy

Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses > 10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy), premedication prior to chemotherapy, or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

Regular concomitant use of bisphosphonates and RANK-L inhibitors for prevention or reduction of skeletal-related events in patients with bone metastases is allowed if initiated prior to first dose of study therapy. Prior palliative radiotherapy must have been completed at least 2 weeks prior to randomization.

3.4.3.1 Palliative Local Therapy

Palliative local therapy, including palliative radiation therapy and palliative surgical resection, to symptomatic non-target bone lesions, skin lesions, or CNS lesions is permitted prior to discontinuation of study treatment for subjects who do not have evidence of overall clinical or radiographic progression per RECIST 1.1. Palliative local therapy to lesions causing hemoptysis may also be permitted prior to discontinuation of study treatment in subjects who do not have evidence of overall clinical or radiographic progression per RECIST 1.1, provided that the lesions undergoing palliative local therapy are not the only sites of measurable disease and the case is discussed with and approved by the Medical Monitor.

Subjects requiring palliative local therapy should be evaluated for objective evidence of disease progression prior to the initiation of such therapy, particularly if the most recent tumor assessment was more than 4 weeks prior to the start of local therapy. If progression per RECIST 1.1 is identified on any tumor assessments prior to the initiation of palliative local therapy, then subjects must either discontinue study drug treatment or they must meet criteria to continue treatment beyond progression (Section 4.5.8) in order to resume immunotherapy after palliative local therapy (Arm A and B). Subjects in Arm C who are found to have progression per RECIST 1.1 on any tumor assessments prior to the initiation of palliative local therapy must discontinue chemotherapy.

The potential for overlapping toxicities with radiotherapy and nivolumab/ipilimumab currently is not known; however, anecdotal data suggests that it is tolerable. As concurrent radiotherapy and nivolumab/ipilimumab have not been formally evaluated, in cases where palliative radiotherapy is required for a tumor lesion, then nivolumab/ipilimumab should be withheld for at least 1 week before, during, and 1 week after radiation. Subjects should be closely monitored for any potential toxicity during and after receiving radiotherapy, and AEs should resolve to Grade ≤ 1 prior to resuming nivolumab.

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 adverse event (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
- Maximum of 24 months (96 weeks) of treatment for nivolumab and ipilimumab

In the case of pregnancy, the investigator must immediately notify the Sponsor or designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). Please contact the Sponsor or designee within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the Sponsor or designee must occur.

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

In this study, PFS is the primary endpoint of the study. Post study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study drug must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

Follow-Up Visit 1 is to occur 35 days from the last dose (± 7 days) or coinciding with the date of discontinuation of study drug (± 7 days) if the date of discontinuation is greater than 42 days from the last dose. Follow-Up Visit 2 is to occur 80 days from Follow-Up Visit 1 (± 7 days). Survival Follow-Up Visits are to occur approximately every 3 months from Follow-Up Visit 2 (± 7 days). Survival Follow-Up Visits may be performed by phone contact or office visit.

BMS may request that survival data be collected on all *randomized* subjects outside of the protocol-defined window (Table 5.1-3). At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contact.

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 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**, if 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

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

- All products, active or placebo, being tested or used as a comparator in a clinical trial.
- Study required premedication, and
- Other drugs administered as part of the study that are critical to claims of efficacy (eg, background therapy, rescue medications)
- If specific criteria are required for treatment in a given phase of the study (e.g. extension phase), provide detailed criteria in this section
- Diagnostic agents: (such as glucose for glucose challenge) given as part of the protocol requirements must also be included in the dosing data collection.

Table 4-1: Study Drugs for CA209722

Product Description / Class and Dosage Form	Potency	IP/ Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
Nivolumab Solution for Injection[a]	100 mg (10 mg/mL)	IP	Open-label	Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8° C. Protect from light and freezing
Ipilimumab Solution for Injection	200 mg (5 mg/mL)	IP	Open-label	Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8° C. Protect from light and freezing
Carboplatin Solution for Injection[b]	450 mg/vial (10 mg/mL)	IP	Open-label	Clear, colorless or slightly yellow solution	Store at or below 25° C Protect from light
Carboplatin Injection (China)	Varies per market product	IP	Open-label	As per market product	Store as indicated on market product
Cisplatin Concentrate for Solution for Infusion[b]	100 mg/vial (1 mg/mL)	IP	Open-label	Clear, colorless solution	Do not store above 25° C. Do not refrigerate or freeze. Store in original container.
Cisplatin Infusion (China)	Varies as per market product	IP	Open-label	As per market product	Store as indicated on market product.
Pemetrexed Powder for Concentrate for Solution for Infusion[b]	500 mg/vial	IP	Open-label	White to either light yellow or green-yellow lyophilized powder	Store at 15 to 25° C.
Pemetrexed Disodium for Injection (China)	500 mg/vial	IP	Open label	As per market product	Store as indicated on market product

[a] May be labeled as either “BMS-936558-01” or “Nivolumab.”

[b] These products may be obtained 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.

In this protocol, investigational products are:

- Nivolumab
- Ipilimumab
- Cisplatin
- Carboplatin
- Pemetrexed

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.

4.3 Storage of Study Drug

The product storage manager should ensure that the study drug 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 or designee immediately.

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

Please refer to Section 9.2.2 for guidance on IP records and documentation.

4.4 Method of Assigning Subject Identification

CA209722 is an open-label, randomized trial. Subjects who experienced progression on 1L or 2L EGFR TKI therapy will be screened for PD-L1. Subjects who failed a 1L first- or second-generation TKI will also be screened for T790M mutation status and only subjects who are negative for T790M mutation will be randomized. After the subject's initial eligibility is established and informed consent has been obtained, the subject must be enrolled into the study by calling the IWRS to obtain the subject number. Every subject that signs the informed consent form must be assigned a subject number in IWRS. Specific instructions for using IWRS will be provided

to the investigational site in a separate document. The investigator or designee will register the subject for enrollment by following the enrollment procedures established by BMS.

The following information is required for enrollment:

- Date that informed consent was obtained
- Date of birth
- Gender at birth

Once enrolled in IWRS, enrolled subjects who have met all eligibility criteria will be ready to be randomized through IWRS. PD-L1 expression data will be transferred directly from analyzing lab to IWRS. The following information is required for subject randomization:

- Subject number
- Date of birth
- EGFR-mutated status (confirmed from tissue sample) for subjects who were treated with osimertinib
- EGFR-mutated , T790M negative status (confirmed from tissue sample) for subjects who were treated with 1L first- or second-generation TKI
- PD-L1 status
- Brain metastases
- Smoking history
- Prior osimertinib use

Subjects meeting all eligibility criteria will be stratified according to PD-L1 status (≥ 1% or < 1% or not evaluable/indeterminate), brain metastases (presence or absence), smoking history (current/former smokers or never smokers), and prior osimertinib use (yes or no). Enrollment of subjects who do not have evaluable or have indeterminate PD-L1 status will be capped at 10%.

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

4.5 Selection and Timing of Dose for Each Subject

The dosing schedule is detailed below Table 4.5-1.

All subjects will be monitored continuously for AEs while on study treatment. Treatment modifications (eg, dose delay, reduction, retreatment, or discontinuation) will be based on specific laboratory and adverse event criteria, as described in Sections 4.5.4, 4.5.5, 4.5.6, 4.5.7, and 4.5.8.

Table 4.5-1: Selection and Timing of Dose for Each Arm

Arm	Week 1	2	3	4	5	6	7 [a]	8	9	10	11	12	13 and Beyond[c]
A	Cycle 1 Day 1 Nivo + Pem/Cis Or Pem/Carbo			Cycle 2 Day 1 Nivo + Pem/Cis Or Pem/Carbo			Cycle 3 Day 1 Nivo + Pem/Cis Or Pem/Carbo			Cycle 4 Day 1 Nivo + Pem/Cis Or Pem/Carbo			Cycle 5 Day 1 Nivo +Pem Q3W[b]
B	Cycle 1 Day 1 Nivo+Ipi		Cycle 2 Day 1 Nivo		Cycle 3 Day 1 Nivo		Cycle 4 Day 1 Nivo+Ipi		Cycle 5 Day 1 Nivo		Cycle 6 Day 1 Nivo		Cycle 7 Day 1 Nivo Q2W/Ipi Q6W
C	Cycle 1 Day 1 Pem/Cis Or Pem/Carbo			Cycle 2 Day 1 Pem/Cis Or Pem/Carbo			Cycle 3 Day 1 Pem/Cis Or Pem/Carbo			Cycle 4 Day 1 Pem/Cis Or Pem/Carbo			Cycle 5 Day 1 Pem Q3W[b]

All agents will be administered on D1 ± 3 days. First dose of study treatment must begin within 7 days of randomization.

[a] Re-biopsy at Week 7 and at disease progression is highly recommended

[b] Maintenance therapy continues until disease progression, discontinuation due to unacceptable toxicity, withdrawal of consent, or study closure.

[c] Nivolumab and nivolumab plus ipilimumab combination will have maximum treatment duration is 24 months (96 weeks).

4.5.1 Nivolumab plus Pemetrexed and Cisplatin or Carboplatin (Arm A)

4.5.1.1 Nivolumab plus Pemetrexed and Cisplatin

Subjects will receive nivolumab at a dose of 360 mg as 30-minute IV infusion on Day 1, followed by pemetrexed at a dose of 500 mg/m^2 as a 10-minute IV infusion or per institutional standard with cisplatin at a dose of 75 mg/m^2 as a 120 minute IV infusion or per institutional standard, of a 3-week treatment cycle, for up to 4 cycles.

At the time of discontinuation of cisplatin, subjects who have not experienced disease progression will continue to receive nivolumab and pemetrexed at the same dose and schedule on Day 1 of a 3-week treatment cycle, unless 1 or both drugs were discontinued earlier due to toxicity. Treatment will continue until progression, unacceptable toxicity, withdrawal of consent, a maximum of 24 months (96 weeks) for nivolumab treatment, or the study ends, whichever occurs first. In subjects who required pemetrexed dose reduction due to toxicity during the pemetrexed/cisplatin combination cycles, the dose of pemetrexed may be escalated to 500 mg/m^2 after the discontinuation of cisplatin at the investigator's discretion and according to local standards, if the prior toxicity was felt to be related mainly to cisplatin.

There will be no dose escalations or reductions of nivolumab allowed. Premedications are not recommended for the first dose of nivolumab.

Participants should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, participants should be managed according to Section 4.5.11.

Doses of nivolumab may be interrupted, delayed, or discontinued depending on how well the subject tolerates the treatment. Dosing visits are not skipped, only delayed.

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) and 40 mg/mL (10 mg/mL) is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding (polyethersulfone membrane) in-line filter at the protocol-specified doses. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 0.35 mg/mL, not to exceed a total infusion volume of 160 mL. For patients weighting less than 40 kg, the total volume of infusion must not exceed 4 mL/kg of patient weight. Instructions for dilution and infusion of nivolumab injection may be provided in the clinical protocol, pharmacy binder, or pharmacy reference sheet. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets and glass bottles.

Dosing calculation for pemetrexed and cisplatin should be based on the body surface area calculation and may be capped per local standards. The dose may remain the same if the subject's weight is within 10% of the baseline weight or prior dose weight. All doses should be rounded up to the nearest milligram or per institutional standard.

Cisplatin will be administered over 120 minutes or per institutional standard following the end of the pemetrexed infusion. Pretreatment hydration for cisplatin can follow local standard of care or use 1 to 2 liters of fluid infused IV for 8 to 12 hours prior to cisplatin infusion is recommended. Adequate hydration and urinary output must be maintained for at least 24 hours following cisplatin administration. Administration and monitoring should be performed according to local standards. Use of mannitol following the cisplatin infusion should also follow local standards of care.

Premedications for use with pemetrexed: Oral corticosteroid should be given according to local standards at a dose equivalent to dexamethasone 4 mg BID on the day prior to, the day of, and the day after the administration of pemetrexed. Oral folic acid 350 to 1000 mcg daily should be given starting 1 week prior to the first dose of pemetrexed, with at least 5 doses of folic acid administered in the 7 days prior to the first dose. Oral folic acid should be continued daily throughout the treatment with pemetrexed and for 21 days after the last dose of pemetrexed. Intramuscular (IM) injection of vitamin B12 1000 mcg should be given approximately 1 week prior to the first dose of pemetrexed and repeated every 3 cycles thereafter during pemetrexed treatment. Subsequent injections of vitamin B12 may be given on the same day as pemetrexed.

Premedications for use with pemetrexed/cisplatin: Antiemetic premedication will be administered according to local standards. Recommended antiemetic treatments are dexamethasone (dosing according to local standards; an equivalent dose of another corticosteroid may be substituted) and a 5-HT3 receptor antagonist (type per investigator discretion and local standard of care). Additional use of antiemetic premedications may be employed at the discretion of the Investigator.

Doses of pemetrexed and/or cisplatin may be interrupted, delayed, reduced, or discontinued depending on how well the subject tolerates the treatment. See Section 4.5.4, 4.5.5, and 4.5.7 for additional details.

All subjects who will be receiving cisplatin should have audiometric testing performed prior to initiation of therapy and prior to subsequent doses of cisplatin, or as per local standards of care.

Subjects who discontinue cisplatin alone may, at the investigator's discretion, be switched to pemetrexed/carboplatin for the remainder of the platinum doublet cycles (up to 4 cycles in total). Dosing for pemetrexed/carboplatin for such subjects should follow the instructions in the Pemetrexed/Carboplatin with Pemetrexed Continuation Maintenance, Section 4.5.3.2.

4.5.1.2 Nivolumab plus Pemetrexed/Carboplatin

Subjects will receive nivolumab at a dose of 360 mg as 30-minute IV infusion on Day 1, followed by pemetrexed at a dose of 500 mg/m^2 as a 10-minute IV infusion or per institutional standard with carboplatin at a dose of AUC 5 or 6 as a 30-minute infusion or per institutional standard, on Day 1 of a 3-week treatment cycle, for up to 4 cycles.

At the time of discontinuation of carboplatin, subjects who have not experienced disease progression will continue to receive nivolumab and pemetrexed at the same dose and schedule on Day 1 of 3-week treatment cycle. Treatment will continue until progression, unacceptable toxicity, withdrawal of consent, a maximum of 24 months (96 weeks) for nivolumab treatment, or the study ends, whichever occurs first. In subjects who required pemetrexed dose reduction due to toxicity

during the pemetrexed/carboplatin combination cycles, the dose of pemetrexed may be escalated to 500 mg/m^2 after the discontinuation of carboplatin, at the investigator's discretion and according to local standards, if the prior toxicity was felt to be related mainly to carboplatin.

There will be no dose escalations or reductions of nivolumab allowed. Premedications are not recommended for the first dose of nivolumab.

Participants should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, participants should be managed according to Section 4.5.11.

Doses of nivolumab may be interrupted, delayed, or discontinued depending on how well the subject tolerates the treatment. Dosing visits are not skipped, only delayed.

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) and 40 mg/mL (10 mg/mL) is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding (polyethersulfone membrane) in-line filter at the protocol-specified doses. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 0.35 mg/mL, not to exceed a total infusion volume of 160 mL. For patients weighting less than 40 kg, the total volume of infusion must not exceed 4 mL/kg of patient weight. Instructions for dilution and infusion of nivolumab injection may be provided in the clinical protocol, pharmacy binder, or pharmacy reference sheet. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets and glass bottles.

Pemetrexed dosing calculations should be based on the body surface area calculation. The dose may remain the same if the subject's weight is within 10% weight used to calculate the previous dose. All doses should be rounded up to the nearest milligram or per institutional standard.

The carboplatin dose will be calculated using the Calvert formula as follows:

Carboplatin dose (mg) = Target AUC x [(CrCl (mL/min) + 25]

Creatinine clearance (CrCl) calculation is based on the Cockroft-Gault formula and should include the most recent serum creatinine and most recent weight. NOTE: If calculation of the CrCl by the Cockroft-Gault formula yields a result of > 125 mL/min, then a CrCl should be calculated by an alternative formula per institutional standards or capped at 125 mL/min.

The carboplatin dose may remain the same if the subject's weight is within 10% of the baseline weight or prior dose weight. The dose of carboplatin may be capped per local standards.

Premedication for use with pemetrexed: Oral corticosteroid should be given according to local standards at a dose equivalent to dexamethasone 4 mg BID on the day prior to, the day of, and the day after the administration of pemetrexed. Oral folic acid 350 to 1000 mcg daily should be given starting 1 week prior to the first dose of pemetrexed, with at least 5 doses of folic acid administered in the 7 days prior to the first dose. Oral folic acid should be continued daily throughout the

treatment with pemetrexed and for 21 days after the last dose of pemetrexed. Intramuscular (IM) injection of vitamin B12 1000 mcg should be given approximately 1 week prior to the first dose of pemetrexed and repeated every 3 cycles thereafter during pemetrexed treatment. Subsequent injections of vitamin B12 may be given on the same day as pemetrexed.

Premedications for use with pemetrexed/carboplatin: Antiemetic premedication will be administered according to local standards. Recommended antiemetic treatments are dexamethasone (dosing according to local standards; an equivalent dose of another corticosteroid may be substituted) and a 5-HT3 receptor antagonist (type per investigator discretion and local standards-of-care). Additional use of antiemetic premedications may be employed at the discretion of the Investigator.

Doses of pemetrexed and/or carboplatin may be interrupted, delayed, reduced, or discontinued depending on how well the subject tolerates the treatment. See Section 4.5.4, 4.5.5, and 4.5.7 for additional details.

Subjects who discontinue carboplatin alone may, at the investigator's discretion, be switched to pemetrexed/cisplatin for the remainder of the platinum doublet cycles (up to 4 cycles in total). Dosing for pemetrexed/cisplatin for such subjects should follow the instructions in the Pemetrexed/Cisplatin with Pemetrexed Continuation Maintenance, Section 4.5.3.1.

4.5.2 Nivolumab plus Ipilimumab (Arm B)

NOTE: As per revised protocol 04, Arm B has closed enrollment.

Subjects randomized to Arm B will receive treatment with nivolumab 3 mg/kg as a 30-minute infusion every 2 weeks and ipilimumab 1 mg/kg as a 30-minute infusion every 6 weeks, starting on Day 1, until progression, unacceptable toxicity, withdrawal of consent, a maximum of 24 months (96 weeks), or the study ends, whichever occurs first.

When study drugs (nivolumab and ipilimumab) are to be administered on the same day, nivolumab is to be administered first. Nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be ipilimumab and will start after the infusion line has been flushed, filters changed, and patient has been observed to ensure no infusion reaction has occurred. The time in between infusions is expected to be approximately 30 minutes but may be more or less depending on the situation.

Dosing calculations should be based on the body weight assessed. 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 up to the nearest milligram or per institutional standard. There will be no dose escalations or reductions allowed.

Subjects may be dosed with nivolumab no less than 12 days from the previous dose. Subjects may be dose with ipilimumab no less than 37 days from the previous dose. There are no premedications recommended.

There will be no dose escalations or reductions of nivolumab or ipilimumab allowed. Premedications are not recommended for the first dose of nivolumab or ipilimumab.

Doses of nivolumab may be interrupted, delayed, or discontinued depending on how well the subject tolerates the treatment. Dosing visits are not skipped, only delayed.

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) and 40 mg/mL (10 mg/mL) is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding (polyethersulfone membrane) in-line filter at the protocol-specified doses. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 0.35 mg/mL, not to exceed a total infusion volume of 160 mL. For patients weighting less than 40 kg, the total volume of infusion must not exceed 4 mL/kg of patient weight. Instructions for dilution and infusion of nivolumab injection may be provided in the clinical protocol, pharmacy binder, or pharmacy reference sheet. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets and glass bottles.

Ipilimumab injection can be used for IV administration without dilution after transferring to a PVC, non-PVC/non-DEHP or glass container and is stable for 24 hours at 2-8°C or room temperature/room light (RT/RL). For ipilimumab storage instructions, refer to ipilimumab IB and/or pharmacy reference sheets.

Separate infusion bags and filters should be used when administering nivolumab and ipilimumab on the same day.

Ipilimumab is to be administered as a 30-minute IV infusion, may be using a volumetric pump with a 0.2 to 1.2 micron in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% normal saline or 5% Dextrose Injection to concentrations between 1 mg/mL and 4 mg/mL. It is not to be administered as an IV push or bolus injections. Care must be taken to assure sterility of the prepared solutions, since the drug product does not contain any antimicrobial preservatives or bacteriostatic agents. At the end of the infusion, flush the line with a sufficient quantity of normal saline or 5% dextrose solution.

Subjects should be carefully monitored for infusion reactions. If an acute infusion reaction is noted, subjects should be managed according to Section 4.5.11.

Doses of nivolumab and/or ipilimumab may be interrupted, delayed, or discontinued depending on how well the subject tolerates the treatment. See Sections 4.5.4.2, 4.5.5.1, 4.5.7.1, and 4.5.7.2 for additional information.

4.5.3 Pemetrexed and Cisplatin or Carboplatin (Arm C)

Subjects randomized to Arm C may receive 1 of the following pemetrexed/platinum regimens, with pemetrexed continuation maintenance therapy.

4.5.3.1 Pemetrexed/Cisplatin With Pemetrexed Continuation Maintenance

Subjects will receive pemetrexed at a dose of 500 mg/m^2 as a 10-minute IV infusion or per institutional standard on Day 1 with cisplatin at a dose of 75 mg/m^2 as a 120-minute IV infusion or per institutional standard on Day 1 of a 3-week treatment cycle for up to 4 cycles.

After Cycle 4, subjects with stable disease or response will discontinue cisplatin and continue pemetrexed at the same dose and schedule as continuation maintenance until progression, unacceptable toxicity, or withdrawal of consent. In subjects who required pemetrexed dose reduction due to toxicity during the pemetrexed/cisplatin combination cycles, the dose of pemetrexed may be escalated to 500 mg/m^2 after the discontinuation of cisplatin, at the investigator's discretion and according to local standards, if the prior toxicity was felt to be related mainly to cisplatin.

Dosing calculations should be based on the body surface area calculation and may be capped per local standards. The dose may remain the same if the subject's weight is within 10% of the baseline weight or prior dose weight. All doses should be rounded up to the nearest milligram or per institutional standard.

Cisplatin will be administered to subjects over 120 minutes or per institutional standard following the end of the pemetrexed infusion. Pretreatment hydration for cisplatin can follow local standard of care, or use 1 to 2 liters of fluid infused IV for 8 to 12 hours prior to cisplatin infusion is recommended. Adequate hydration and urinary output must be maintained for at least 24 hours following cisplatin administration. Administration and monitoring should be performed according to local standards. Use of mannitol following the cisplatin infusion should also follow local standard of care.

Premedications for use with pemetrexed: Oral corticosteroid should be given according to local standards at a dose equivalent to dexamethasone 4 mg BID on the day prior to, the day of, and the day after the administration of pemetrexed. Oral folic acid 350 to 1000 mcg daily should be given starting 1 week prior to the first dose of pemetrexed, with at least 5 doses of folic acid administered in the 7 days prior to the first dose. Oral folic acid should be continued daily throughout the treatment with pemetrexed and for 21 days after the last dose of pemetrexed. Intramuscular (IM) injection of vitamin B12 1000 mcg should be given approximately 1 week prior to the first dose of pemetrexed repeated every 3 cycles thereafter during pemetrexed treatment. Subsequent injections of vitamin B12 may be given on the same day as pemetrexed.

Premedications for use with pemetrexed/cisplatin: Antiemetic premedication will be administered according to local standards. Recommended antiemetic treatments are dexamethasone (dosing according to local standards; an equivalent dose of another corticosteroid may be substituted) and a 5-HT3 receptor antagonist (type per investigator discretion and local standards of care). Additional use of antiemetic premedications may be employed at the discretion of the Investigator.

Doses of pemetrexed and/or cisplatin may be interrupted, delayed, reduced, or discontinued depending on how well the subject tolerates the treatment. See Section 4.5.4, 4.5.5, and 4.5.7 for additional details.

All subjects who will be receiving cisplatin should have audiometric testing performed prior to initiation of therapy and prior to subsequent doses of cisplatin, or as per local standards of care.

Subjects who discontinue cisplatin alone may, at the investigator's discretion, be switched to pemetrexed/carboplatin for the remainder of the platinum doublet cycles (up to 4 cycles in total). Dosing for pemetrexed/carboplatin for such subjects should follow the instructions in the pemetrexed/carboplatin with pemetrexed continuation maintenance Section 4.5.3.2.

4.5.3.2 Pemetrexed/Carboplatin With Pemetrexed Continuation Maintenance

Subjects will receive pemetrexed at a dose of 500 mg/m^2 as a 10-minute IV infusion or per institutional standard on Day 1, followed by carboplatin at a dose of AUC 5 or 6 as a 30-minute IV infusion or per institutional standard, on Day 1 of a 3-week treatment cycle for up to 4 cycles.

After Cycle 4, subjects with stable disease or response will discontinue carboplatin and continue pemetrexed at the same dose and schedule as continuation maintenance until progression, unacceptable toxicity, or withdrawal of consent. In subjects who required pemetrexed dose reduction due to toxicity during the pemetrexed/carboplatin combination cycles, the dose of pemetrexed may be escalated to 500 mg/m^2 after the discontinuation of carboplatin, at the investigator's discretion and according to local standards, if the prior toxicity was felt to be related mainly to carboplatin.

Pemetrexed dosing calculations should be based on the body surface area calculation. The dose may remain the same if the subject's weight is within 10% weight used to calculate the previous dose. All doses should be rounded up to the nearest milligram or per institutional standard.

The carboplatin dose will be calculated using the Calvert formula as follows:

- Carboplatin dose (mg) = Target AUC x [(CrCl (mL/min) + 25]
- Creatinine clearance (CrCl) calculation is based on the Cockroft-Gault formula and should include the most recent serum creatinine and most recent weight. NOTE: If calculation of the CrCl by the Cockroft-Gault formula yields a result of > 125 mL/min, then a CrCl should be calculated by an alternative formula per institutional standards or capped at 125 mL/min.
- The dose of carboplatin may be capped per local standards

Premedication for use with pemetrexed: Oral corticosteroid should be given according to local standards at a dose equivalent to dexamethasone 4 mg BID on the day prior to, the day of, and the day after the administration of pemetrexed. Oral folic acid 350 to 1000 mcg daily should be given starting 1 week prior to the first dose of pemetrexed, with at least 5 doses of folic acid administered in the 7 days prior to the first dose. Oral folic acid should be continued daily throughout the treatment with pemetrexed and for 21 days after the last dose of pemetrexed. IM injection of vitamin B12 1000 mcg should be given approximately 1 week prior to the first dose of pemetrexed and repeated every 3 cycles thereafter during pemetrexed treatment. Subsequent injections of vitamin B12 may be given on the same day as pemetrexed.

Premedications for use with pemetrexed/carboplatin: Antiemetic premedication will be administered according to local standards. Recommended antiemetic treatments are dexamethasone (dosing according to local standards; an equivalent dose of another corticosteroid may be substituted) and a 5-HT3 receptor antagonist (type per investigator discretion and local standards-of-care). Additional use of antiemetic premedications may be employed at the discretion of the Investigator.

Doses of pemetrexed and/or carboplatin may be interrupted, delayed, reduced, or discontinued depending on how well the subject tolerates the treatment. See Section 4.5.4, 4.5.5, and 4.5.7 for additional details.

Subjects who discontinue carboplatin alone may, at the investigator's discretion, be switched to pemetrexed/cisplatin for the remainder of the platinum doublet cycles (up to 4 cycles in total). Dosing for pemetrexed/cisplatin for such subjects should follow the instructions in the pemetrexed/cisplatin with pemetrexed continuation maintenance Section 4.5.3.1.

4.5.4 Dose Delay Criteria

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

4.5.4.1 Dose Delay Criteria for Arm A (Nivolumab plus Platinum-Doublet Chemotherapy)

In Arm A, dosing of all drugs should be delayed if any criteria in Sections 4.5.4.2 or 4.5.4.3 are met.

4.5.4.2 Dose Delay for Arm B (Nivolumab plus Ipilimumab)

Nivolumab and ipilimumab administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related adverse event, except for fatigue and laboratory abnormalities
- Any Grade ≥ 3 skin drug-related AE
- Any Grade ≥ 3 drug-related laboratory abnormality with the following exceptions for lymphopenia, AST, ALT, or total bilirubin or asymptomatic amylase or lipase:
  - Grade 3 lymphopenia does not require a dose delay
  - If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity
  - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity
  - Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay.
- Any AE, laboratory abnormality or inter-current illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Subjects receiving ipilimumab in combination with nivolumab that have drug-related toxicities that meet the criteria for dose delay should have both drugs (ipilimumab and nivolumab) delayed

until retreatment criteria are met. (Exceptions apply to the retreatment criteria after dose delay of ipilimumab and nivolumab for Grade ≥ 3 amylase and lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and that are attributed to ipilimumab alone.)

- Nivolumab may be delayed until the next planned ipilimumab dose if the next ipilimumab dose is scheduled within the next 12 days. This will permit periodic ipilimumab dosing to be synchronized with nivolumab dosing.
- Ipilimumab should be dosed at the specified interval regardless of any delays in intervening nivolumab doses. However, in order to maintain periodic synchronized dosing of ipilimumab and nivolumab, the dosing days of nivolumab and ipilimumab may be adjusted within the permitted ± 5 day window, as long as consecutive nivolumab doses are given at least 12 days apart. Ipilimumab may be delayed beyond the 5-day window if needed to synchronize with the next nivolumab dose.
- If an ipilimumab dose is delayed beyond 6 weeks from the prior ipilimumab dose, then subsequent ipilimumab doses should be rescheduled to maintain the 6-week interval between consecutive ipilimumab doses.
- A dose delay of ipilimumab which results in no ipilimumab dosing for > 12 weeks requires ipilimumab discontinuation, with exceptions as noted in Section 4.5.6.2.

4.5.4.3 Dose Delay Criteria for Platinum Doublet Chemotherapy

In Arms A and C, dosing of both drugs in the platinum doublet chemotherapy regimen selected should be delayed for any of the following on the Day 1 of each cycle:

- Absolute neutrophil count (ANC) < 1500/μL
- Platelets < 100,000/mm^3
- Any Grade ≥ 2 non-skin, non-hematologic, drug-related adverse event (excluding Grade 2 alopecia, Grade 2 fatigue, and Grade 2 laboratory abnormalities)
- Any Grade ≥ 3 skin, drug-related adverse event
- Any Grade ≥ 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, AST, ALT, or total bilirubin:
  - Grade 3 lymphopenia does not require dose delay.
  - If a subject has a baseline AST, ALT or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity.
  - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication. Investigators should consult local labeling for the chemotherapy drugs being administered to any given subject for additional guidance on dose delays.

In addition, subjects receiving cisplatin with pemetrexed must discontinue cisplatin if the calculated creatinine clearance decreases to < 50 mL/min (based on the Cockroft Gault formula) and discontinue pemetrexed if the calculated creatinine clearance decreases to <45 mL/min. Pemetrexed may be continued, and the platinum agent may, at the investigator's discretion, be switched to carboplatin for the remainder of the platinum doublet cycles (up to 4 cycles in total) as specified in Section 4.5.6.3 and Section 4.5.7.3.

If any non-hematologic adverse event meeting the dose delay criteria above is felt to be related to only 1 particular agent in the platinum doublet chemotherapy regimen, then that agent alone may be omitted for that cycle while the other agent is given. In order to maintain synchronized dosing of the regimen, the omitted agent should be resumed with the next scheduled cycle once the AE has improved and retreatment criteria are met. Please refer to Section 4.5.4.3 to determine if dose reduction of the resumed agent is required.

If both drugs in the platinum doublet chemotherapy regimen are delayed, then the subject should be re-evaluated weekly or more frequently if clinically indicated until re-treatment criteria are met (as per Section 4.5.6.3).

4.5.5 Dose Reductions

4.5.5.1 Dose Reductions for Nivolumab or Ipilimumab

There will be no dose reductions for nivolumab or ipilimumab

4.5.5.2 Dose Reductions for Platinum Doublet Chemotherapy

Dose reductions of platinum doublet chemotherapy may be required and will be performed according to Table 4.5.5.2-1. The dosing reduction criteria will apply to Arms A and C. Chemotherapy dose reductions are permanent; once the dose of any chemotherapy agent is reduced, it may not be re-escalated in subsequent cycles, except as noted when starting pemetrexed maintenance therapy. The dose reductions for each agent in the platinum doublet chemotherapy regimen are not linked and may be adjusted independently as summarized below.

Any subjects with 2 prior dose reductions for one agent who experiences a toxicity that would cause a third dose reduction must be discontinued from that agent.

Table 4.5.5.2-1: Dose Modification of Chemotherapeutic Agents

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

Dose Reductions for Hematologic Toxicity

Dose modifications for hematologic toxicities (according to CTCAE version 4) are summarized in Table 4.5.5.2-2. Dose adjustments are based on nadir blood counts (assessed as per local standards) since the preceding drug administration. Dose level adjustments for platinum doublet chemotherapy are relative to that of the preceding administration. Generally, both chemotherapy agents in the platinum doublet chemotherapy regimen should be dose reduced together for hematologic toxicity. 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 4.5.5.2-2: Dose Modifications for Hematologic Toxicity (based on nadir counts)

Toxicity	Pemetrexed	Cisplatin	Carboplatin
Neutrophil Count Decreased			
Grade 4 ($< 500/mm^3$ or $< 0.5 \times 10^9/L$)	Reduce one dose level	Reduce one dose level	Reduce one dose level
Platelet Count Decreased			
Grade 3 ($50,000/mm^3$; 25.0 to $< 50.0 \times 10^9/L$)	Reduce one dose level	Reduce one dose level	Reduce one dose level
Grade 4 ($< 25,000/mm^3$; $< 25.0 \times 10^9/L$)	Reduce one dose level	Reduce one dose level	Reduce one dose level

Dose Reductions for Non-Hematologic Toxicities

Dose adjustments for platinum doublet chemotherapy for non-hematologic toxicities during treatment are described in Table 4.5.5.2-3. All dose reductions should be made based on the worst grade toxicity. Subjects experiencing any of the toxicities detailed in Table 4.5.5.2-3 during the previous cycle should have their chemotherapy delayed until retreatment criteria are met (per Section 4.5.6.3) and then reduced for all subsequent cycles by 1 dose level or discontinued as appropriate. Dose levels for the 2 drugs in the platinum-doublet chemotherapy regimen are not linked and may be reduced independently, as summarized in the table below.

Table 4.5.5.2-3: Non-hematologic Toxicity Dose Reductions

Toxicity	Pemetrexed	Cisplatin	Carboplatin
Febrile Neutropenia Grade ≥ 3	Reduce one dose level	Reduce one dose level	Reduce one dose level
Diarrhea Grade ≥ 3	Reduce one dose level	No change	No change

Table 4.5.5.2-3: Non-hematologic Toxicity Dose Reductions			
Toxicity	**Pemetrexed**	**Cisplatin**	**Carboplatin**
Allergic reaction[a] Grade ≥ 3	Discontinue	Discontinue	Discontinue
Neuropathy Grade 2	No change	Reduce one dose level	No change
Neuropathy Grade ≥ 3	Discontinue	Discontinue	Discontinue
Calculated creatinine clearance < 50 mL/min	Discontinue if creatinine clearance < 45 mL/mon	Discontinue	Discontinue if creatinine clearance < 20 mL/min
Other Grade ≥ 3 toxicity (except for fatigue and transient arthralgia and myalgia)	Adjust as medically indicated	Adjust as medically indicated	Adjust as medically indicated

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

4.5.6 Criteria to Resume Dosing

4.5.6.1 Criteria to Resume Nivolumab Dosing

Subjects may resume treatment with nivolumab when the 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 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 4.5.4.2) should have treatment permanently discontinued.
- For subjects with Grade 2 AST, ALT, OR TBILI elevations, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Subjects 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 the Medical Monitor.
- Subjects who received systemic corticosteroids for management of any drug-related toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone ≤ 10 mg/day.

- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the Medical Monitor.
- Subjects who delay study treatment due to any Grade ≥ 3 amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis, and that is assessed by the investigator to be related to ipilimumab and not to nivolumab, may resume nivolumab when the amylase or lipase abnormality has resolved to Grade < 3. The Medical Monitor should be consulted prior to resuming nivolumab in such subjects.

4.5.6.2 Criteria to Resume Ipilimumab Dosing

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

- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT or total bilirubin.
- Subjects with combined Grade 2 AST/ALT and total bilirubin values meeting discontinuation parameters (Section 4.5.7.2) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed.
- Subjects who received systemic corticosteroids for management of any drug-related toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone ≤ 10 mg/day.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the Medical Monitor.
- Dose delay of ipilimumab which results in no ipilimumab dosing for > 12 weeks requires ipilimumab discontinuation, with exceptions as noted in Section 4.5.6.2.
- Ipilimumab may not be resumed sooner than 6 weeks (± 5 days) after the prior ipilimumab dose.
- In general, subjects who meet criteria to resume ipilimumab will also have met criteria to resume nivolumab, so it should be feasible to synchronize dosing of both drugs when resuming ipilimumab. In order to facilitate this, the dosing days of nivolumab and ipilimumab may be adjusted within the permitted ± 5 day window, as long as consecutive nivolumab doses are given at least 12 days apart.
- One exception to note is when ipilimumab and nivolumab doses are delayed due to drug-related Grade ≥ 3 amylase or lipase abnormalities not associated with symptoms or clinical manifestations of pancreatitis. If the investigator assesses the Grade ≥ 3 amylase or lipase abnormality to be related to ipilimumab and not related to nivolumab, nivolumab may be resumed when the amylase or lipase abnormality resolves to Grade < 3 but ipilimumab may only be resumed when the amylase or lipase abnormality resolves to Grade 1 or baseline.

Investigator attribution of this toxicity to the ipilimumab dosing must be clearly noted in the subject's medical chart. The Medical Monitor should be consulted prior to resuming nivolumab in such subjects.

4.5.6.3 Criteria to Resume Platinum Doublet Chemotherapy Dosing

- Subjects may resume treatment with platinum doublet chemotherapy when the ANC returns to ≥ 1500/μL, the platelet count returns to ≥ 100,000/mm^3, and all other drug-related toxicities have returned to baseline or Grade ≤ 1 (or Grade ≤ 2 for alopecia and fatigue).
- If a subject fails to meet criteria for reinitiating treatment, then treatment should be delayed, and the subject should be re-evaluated weekly or more frequently as clinically indicated. Any subject who fails to recover from toxicity attributable to platinum doublet chemotherapy to baseline or Grade ≤ 1 (except Grade 2 alopecia and fatigue) within 6 weeks from the last dose given should discontinue the drug(s) that caused the delay.
- When resuming platinum doublet chemotherapy treatment, please follow the dose reduction recommendations in Section 4.5.5.2.

4.5.7 Treatment Discontinuation Criteria

For all subjects, global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration' in the source data and in the case report form. Every effort should be made to document objective progression (ie, radiographic confirmation) even after discontinuation of treatment.

4.5.7.1 Nivolumab Dose Discontinuation

Treatment with nivolumab should be permanently discontinued for any of the following:

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the treatment re-initiation period OR requires systemic treatment
- Any Grade ≥ 2 drug-related pneumonitis or interstitial lung disease that does not resolve to dose delay and systemic steroids (also see Pulmonary Adverse Event Management Algorithm)
- Any Grade 3 drug-related bronchospasm, hypersensitivity reaction, or infusion reaction, regardless of duration
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, myocarditis (also see Mycoarditis Management Algorithm), hypersensitivity reactions, infusion reactions, endocrinopathies, and laboratory abnormalities:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, 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.
  - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation (also see Hepatic Adverse Event Management Algorithm):
    - AST or ALT > 5-10 × ULN for > 2 weeks
    - AST or ALT > 10 × ULN
    - Total bilirubin > 5 × ULN
    - Concurrent AST or ALT > 3 x ULN **and** total bilirubin > 2 × ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events, which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia
  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to < Grade 4 within 1 week of onset. The Medical Monitor should be consulted for Grade 4 amylase or lipase abnormalities
  - 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 adrenal insufficiency, 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 Medical Monitor.
- Dosing delay of nivolumab which results in treatment interruption of > 6 weeks requires treatment 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 Medical Monitor 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 Medical Monitor. Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks, the Medical Monitor 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 adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.

The assessment for discontinuation of nivolumab should be made separately from the assessment made for discontinuation of ipilimumab. Although there is overlap among the discontinuation criteria, if discontinuation criteria are met for ipilimumab but not for nivolumab, treatment with nivolumab may continue if ipilimumab is discontinued.

If a subject in the nivolumab/ipilimumab combination arm meets criteria for discontinuation and investigator is unable to determine whether the event is related to one or both study drugs, the subject should discontinue both nivolumab and ipilimumab and be taken off the treatment phase of the study.

The assessment for discontinuation of nivolumab should be made separately from the assessment made for discontinuation of chemotherapy doublet. If criteria for discontinuation for nivolumab are met before the nivolumab plus platinum doublet chemotherapy cycles have been completed, platinum doublet chemotherapy may continue until 4 cycles (maximum) have been given.

4.5.7.2 Ipilimumab Dose Discontinuation

Ipilimumab should be permanently discontinued if any of the following criteria are met:

- Any Grade ≥ 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks OR requires systemic treatment;
- Any Grade ≥ 3 bronchospasm or other hypersensitivity reaction;
- Any other Grade 3 non-skin, drug-related adverse with the following exceptions for laboratory abnormalities, Grade 3 nausea and vomiting, Grade 3 neutropenia and thrombocytopenia, and symptomatic endocrinopathies which resolved (with or without hormone substitution);
- Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
  - AST or ALT > 8 × ULN
  - Total bilirubin > 5 ×ULN
  - Concurrent AST or ALT > 3 × ULN and total bilirubin > 2 × ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events, which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia
  - Isolated Grade 4 amylase or lipase abnormalities which are not associated with symptoms or clinical manifestations of pancreatitis. The Medical Monitor should be consulted for Grade 4 amylase or lipase abnormalities
  - 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 adrenal insufficiency, 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 Medical Monitor.

- Any treatment delay resulting in no ipilimumab dosing for > 12 weeks with the following exceptions:
  - Dosing delays to manage drug-related adverse events, such as prolonged steroid tapers, are allowed. Prior to re-initiating treatment in a subject with a dosing delay lasting > 12 weeks, the Medical Monitor must be consulted. **Tumor assessments should continue as per protocol even if dosing is delayed.**
  - Dosing delays lasting > 12 weeks from the previous dose that occur for non-drug related reasons may be allowed if approved by the Medical Monitor. Prior to re-initiating treatment in a subject with a dosing delay lasting > 12 weeks, the Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing
- The assessment for discontinuation of ipilimumab should be made separately from the assessment made for discontinuation of nivolumab. Although there is overlap among the discontinuation criteria, if discontinuation criteria are met for ipilimumab but not for nivolumab, treatment with nivolumab may continue if ipilimumab is discontinued.
- If a subject in the nivolumab/ipilimumab combination arm meets criteria for discontinuation and investigator is unable to determine whether the event is related to both or one study drug, the subject should discontinue both nivolumab and ipilimumab and be taken off the treatment phase of the study.

4.5.7.3 Platinum Doublet Chemotherapy Dose Discontinuation

Except where specified below, both chemotherapy drugs in the platinum doublet chemotherapy regimen should be discontinued for any of the following (applies to Arms A and C):

- 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 x ULN for > 2 weeks
  - AST or ALT > 10 x ULN
  - Total bilirubin > 5 x ULN
  - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Any cisplatin-related decrease in creatinine clearance to < 50 mL/min (using the Cockroft Gault formula) requires discontinuation of cisplatin.
- Any drug-related adverse event which recurs after 2 prior dose reductions for the same drug-related adverse event (as specified in Section 4.5.5.2) 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 adverse event 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 Medical Monitor. Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks, the Medical Monitor 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 adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued platinum doublet chemotherapy dosing. Investigators should consult local labeling for the chemotherapy drugs being administered to any given subject for additional guidance on dose discontinuation.
- A total of 4 cycles of chemotherapy should be given prior to starting pemetrexed maintenance treatment. However, subjects who experience Grade 4 treatment-related hematologic toxicity, or Grade 3 treatment-related non-hematologic toxicity, may start maintenance therapy after 3 cycles of chemotherapy. The nature and grade of the toxicity must be clearly noted, and the medical monitor must be notified.
- Note that subjects receiving pemetrexed/cisplatin who discontinue cisplatin alone may, at the investigator's discretion, be switched to pemetrexed/carboplatin for the remainder of the platinum doublet cycles (up to 4 cycles in total). Subjects receiving pemetrexed/carboplatin who discontinue carboplatin alone may, at the investigator's discretion, be switched to pemetrexed/cisplatin for the remainder of the platinum doublet cycles (up to 4 cycles in total).
- Pemetrexed should not be administered if the calculated CrCl is < 45 mL/min.

4.5.8 Treatment Beyond Disease Progression (Arms A and B)

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[32]

Subjects will be permitted to continue on nivolumab (Arm A) or nivolumab + ipilimumab (Arm B) for treatment beyond initial RECIST 1.1-defined PD as long as they meet the following criteria:

- Investigator-assessed clinical benefit and no rapid disease progression
- Subject is tolerating treatment
- Stable performance status

- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
- **Subject provides written informed consent prior to receiving additional nivolumab and or ipilimumab treatment, using an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options**.

The decision to continue treatment beyond initial investigator-assessed progression must be discussed with the Medical Monitor and documented in the study records. A follow-up scan should be performed within six (6) weeks ± 7 days of original PD to determine whether there has been a decrease in the tumor size, or continued progression of disease.

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 subject continues to achieve clinical benefit by continuing treatment, the subject should remain on the trial and continue to receive monitoring according to the Time and Events Schedule on Table 5.1-2.

For the subjects in Arms A and B who continue study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden from time of initial PD. This includes an increase in the sum of diameters of all target lesions and/ or the diameters of new measurable lesions compared to the time of initial PD. Nivolumab and/or ipilimumab treatment should be discontinued permanently upon documentation of further 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 measurable 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). In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of new lesions which become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

4.5.9 Nivolumab and Ipilimumab Maximum Duration of 24 Months

- Subjects treated on nivolumab (Arm A) or nivolumab plus ipilimumab (Arm B) may receive a maximum treatment duration of 24 months (96 weeks).

4.5.10 Management Algorithms for Immuno-Oncology Agents

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab and ipilimumab are considered immuno-oncology agents in this protocol. Early recognition and management of AEs associated with

immuno-oncology agents may mitigate severe toxicity. Management Algorithms have been developed to assist investigators in assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Myocarditis
- Endocrinopathy
- Skin
- Neurological

The above algorithms are found in the nivolumab Investigator Brochure and in Appendix 2.

4.5.11 Treatment of Nivolumab or Ipilimumab Infusion Reactions

Since nivolumab and ipilimumab contain only human immunoglobulin protein sequences, they are 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, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the Medical Monitor and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE (Version 4) guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

For Grade 1 symptoms: (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 or ipilimumab administrations.

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 or ipilimumab 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 or ipilimumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF).

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 or ipilimumab infusions. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

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 or ipilimumab. 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 or ipilimumab 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).

4.6 Blinding/Unblinding

Not applicable.

4.7 Treatment Compliance

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

4.8 Destruction or Return of Investigational Product

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

If...	Then...
IP supplied by BMS (including its vendors)	Any unused IP supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless IP containers must be immediately

If...	Then...
	destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). If IP will be returned, the return will be arranged by the responsible Study Monitor.
IP sourced by site, not supplied by BMS (or its vendors) (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal, 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. The following minimal standards must be 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.

It is the investigator's or designee's responsibility to arrange for disposal of all empty containers.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of IP provided by BMS (or its vendors). Destruction of non-IP sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

Please refer to Section 9.2.2 for additional guidance on IP records and documentation.

4.9 Retained Samples for Bioavailability / Bioequivalence

Not Applicable.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Procedures (CA209722)

Procedure	Screening Visit Within 28 days prior to randomization (unless otherwise noted). ICF can be obtained and a fresh biopsy can be done within 42 days prior to randomization.	Notes
Eligibility Assessments		
Informed Consent	X	Original IC in screening for protocol participation; Study allows for re-enrollment of a subject that has discontinued the study as a pre-treatment failure. If re-enrolled, the subject must be re-consented and assigned a new subject number from IWRS.
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening and confirmed prior to first dose
Medical History	X	Including smoking history.
PD-L1 and T790M Tumor Tissue Testing	X	Availability of tumor samples prior to therapy is mandatory. A recent archived biopsy (preferably within 6 months of the first dose of the study treatment) or a fresh biopsy are required. If the only available achieved biopsy is more than 6 months prior to the first dose of the study treatment, approval from Medical Monitor is required. For 1L (first- or second-generation) TKI-treated subjects, initial testing of blood samples is allowed in local laboratories using assays approved by local Health Authority only to rule out T790M+ subjects. For T790M negative status, a confirmatory test will be performed centrally or locally using the cobas® EGFR Mutation Test v2 (US-IVD) on tumor tissues. Sufficient tumor tissue obtained before start of study treatment in the metastatic setting or from an unresectable site (block or minimum of 12 slides, obtained from core biopsy, punch biopsy, excisional biopsy or surgical specimen) required for PD-L1 and confirmation of T790M negative status. For subjects where a biopsy is not feasible, archival tumor material must be made available.

Table 5.1-1: Screening Procedures (CA209722)		
Procedure	**Screening Visit** Within 28 days prior to randomization (unless otherwise noted). ICF can be obtained and a fresh biopsy can be done within 42 days prior to randomization.	**Notes**
Screening/baseline tumor assessments	X	CT/MRI of Brain, Chest, Abdomen, Pelvis and all other known sites of disease within 28 days prior to randomization. MRI is preferred; CT with contrast is acceptable for brain imaging. If brain metastases were diagnosed at screening, the screening period can be extended up to 6 weeks to accommodate the treatment and recovery of brain metastases. Further extension of screening period requires approval of Medical Monitor. Tumor assessments following RECIST 1.1 criteria.
Prior cancer therapy	X	Dates, doses, response and duration of 1L or 2L EGFR TKI therapy and prior medications subjects received to treat cancers
ECOG Performance Status	X	Within 14 days of first dose
ECG (12-lead)	X	Obtained only for subjects who have met all eligibility criteria
Safety Assessments		
Physical Examination	X	Height, weight, body surface area within 14 days of first dose.
Vital Signs	X	Including BP, HR, and temperature. Obtain vital signs at the screening visit (within 14 days prior to first dose)
Assessment of Signs and Symptoms	X	Within 14 days of first dose
Serious Adverse Events Assessment	X	
Concomitant Medication Collection	X	Within 14 days prior to first dose through the study period.
Laboratory Tests	X	CBC with differential, chemistry panel including albumin, LDH, LFTs (AST, ALT, total bilirubin, alkaline phosphatase) BUN or serum urea level,

Table 5.1-1: Screening Procedures (CA209722)		
Procedure	**Screening Visit** Within 28 days prior to randomization (unless otherwise noted). ICF can be obtained and a fresh biopsy can be done within 42 days prior to randomization.	**Notes**
		creatinine, Ca, Mg, Na, K, Cl, phosphate, glucose, amylase, lipase, TSH, Free T4, Free T3, within 14 days prior to first dose. Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody (HBcAb), reflex HBV DNA, hepatitis C RNA (HCV RNA), and reflex hepatitis C antibody (HCV Ab). Within 28 days prior to randomization. Thyroid function test including TSH, free T3, and free T4 within 14 days prior to first dose for Arm A only.
Pregnancy Test	X	Serum or urine within 24 hours of first dose.
IWRS		
Enrollment in IWRS	X	For subject number assignment at the time the informed consent is obtained.
Randomize	X	Study treatment must begin within 7 days of randomization.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Ca, calcium, CBC, complete blood count, Cl, chlorine; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor; IWRS, interactive web response system; K, potassium; LDH, lactate dehydrogenase; Mg, magnesium, MRI, magnetic resonance imaging; Na, sodium; TSH, thyroid stimulating hormone.

Table 5.1-2: On-treatment Procedural Outline (CA209722)[a]

Procedure	During Treatment Visit[b,c]	Notes
Safety Assessments		
Targeted Physical Examination	X	
Vital Signs	X	Including BP, HR, and temperature.
Physical Measurements (including performance status)	X	Weight and ECOG status. The dosing calculations should be based on the body weight. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated.
Assessment of Signs and Symptoms	X	
Concomitant Medication Collection	X	
Serious Adverse Event Assessment	X	
Adverse Events Assessment	X	
Laboratory Tests	X	On-study local laboratory assessments should be done within 3 days prior to each dose starting at C1D1. If laboratory tests for screening are done within 3 days prior to each dose starting at C1D1, this screening data can be also used as C1D1 data. CBC w/differential, albumin, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, phosphate, LDH, glucose, amylase, and lipase. Arms A and B only: TSH every 6 weeks (reflex free T3 and T4).
Pregnancy Test	X	Serum or urine within 24 hours prior to first dose and then Day 1 of each cycle
Efficacy Assessments		
Tumor Assessment	X	The first tumor assessments should occur at Week 7 (± 7 days), and then every 6 weeks (±7 days) for the first 49 weeks, then every 12 weeks (± 7 days) per RECIST 1.1 until disease progression or

Table 5.1-2: On-treatment Procedural Outline (CA209722)[a]

Procedure	During Treatment Visit[b,c]	Notes
		treatment is discontinued (if still receiving treatment beyond disease progression) whichever occurs later. Tumor assessments should include CT/MRI of the chest, abdomen, pelvis, and all other known sites of disease. Use same imaging method as was used at screening/baseline. Subjects with a current or past brain metastasis should have surveillance MRI (preferred) or CT with contrast approximately every 12 weeks or sooner if clinically indicated. Refer to Section 5.4 and CA209722 Imaging Manual for further instructions.
Outcomes Research Assessments		
EQ-5D-3L and LCSS	See note	Assessments performed after randomization PRIOR to first dose (Day -3 to Day 1). For on-study visits: Assessments (LCSS and EQ-5D-3L) will be performed on Day 1 of each cycle PRIOR to any study procedures and treatment for the first 6 months on study, then every second cycle thereafter for the remainder of the treatment period.
[redacted]		

Table 5.1-2: On-treatment Procedural Outline (CA209722)[a]

Procedure	During Treatment Visit[b,c]	Notes
Study Drug		
IWRS Drug vial assignment	X	
Dispense Study Drug		Within 7 days of randomization, the subject must receive the first dose of study medication. Subjects may be dosed no less than 19 days between doses during administration of Arms A and C. In Arm B, nivolumab may be dosed no less than 12 days and ipilimumab may be dosed no less than 37 days. Variations to this schedule because of holidays or travel should be discussed with the Medical Monitor.

[a] All assessments should be conducted within 72 hours prior to each dose, unless otherwise specified.

[b] [c] Nivo/ipi Arm (Arm B):occurs every 2 weeks

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Ca, calcium, CBC, complete blood count, Cl, chlorine; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; K, potassium; IWRS, interactive web response system, LCSS, Lung Cancer Symptom Scale; LDH, lactate dehydrogenase; Mg, magnesium, MRI, magnetic resonance imaging; Na, sodium; [redacted] TSH, thyroid stimulating hormone.

Table 5.1-3: Follow-up Procedural Outline (CA209722)

Procedure	Follow-up Visits 1 and 2[a,b]	Survival Follow-up Visits	Notes
Safety Assessments			
Targeted Physical Examination	X		To assess for potential late emergent study drug-related issues
Vital Signs	X		
Assessment of Signs and Symptoms	X		
Serious Adverse Events Assessment	X		See Section 6.1.1
Adverse Events Assessment	X		In survival period only to include toxicities from study therapy. For IMAEs, see Section 6.7.1
Laboratory Tests	X		CBC w/ differential, albumin, LFTs, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, phosphate, LDH, glucose, amylase, and lipase, and TSH (+ reflex Free T4 and Free T3). Thyroid function test will apply to Arms A and B only. To be done at FU1, to be repeated at FU2, if study related toxicity persists.
Review of Concomitant Medications	X	X	Document Subsequent Cancer Therapy
Pregnancy Test (WOCBP only)	X		Serum or urine
[redacted]			
Survival Status			
Survival Status	X	X	Every 3 months after FU 2; may be accomplished by visit, phone contact or email, to assess subsequent anti-cancer therapy Additional subsequent cancer therapy details such as regimen, setting of the regimen, line of therapy, start date and end date of each regimen, best response to the regimen and date of progression after next line therapy will be collected.

Table 5.1-3: Follow-up Procedural Outline (CA209722)

Procedure	Follow-up Visits 1 and 2[a,b]	Survival Follow-up Visits	Notes
Efficacy Assessments			
Tumor Assessment	X	X	Only for subjects without progression and no longer receiving study therapy. The first tumor assessments should occur at Week 7 (±7 days), and then subsequent assessments should occur every 6 weeks (± 7 days) for the first 49 weeks, then every 12 weeks (± 7 days) until disease progression confirmed by BICR (if clinically feasible). Tumor assessments should include CT/MRI of chest, abdomen, pelvis, and all other known sites of disease. Use same imaging method as was used at screening/baseline. Subjects with a current or past brain metastasis should have surveillance MRI (preferred) or CT with contrast approximately every 12 weeks, or sooner if clinically indicated. Refer to Section 5.4 and CA209722 Imaging Manual for further instructions.
Outcomes Research Assessment			
EQ-5D-3L	X	X	In Survival Visits, EQ-5D-3L is collected every 3 months from Follow-up Visit 2 for the first year of the Follow-up Phase, then every 6 months thereafter.
LCSS	X		

[a] Follow-Up Visit 1 is to occur 35 days from the last dose (±7 days) or coinciding with the date of discontinuation of study drug (±7 days) if the date of discontinuation is greater than 42 days from the last dose. Follow-Up Visit 2 is to occur 80 days from Follow-Up Visit 1 (±7 days).

[b] Survival Follow-Up Visits are to occur approximately every 3 months (±7 days) from Follow-Up Visit 2. Survival Follow-Up Visits may be performed by phone contact or office visit.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Ca, calcium, CBC, complete blood count, Cl, chlorine; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; K, potassium; IWRS, interactive web response system, LCSS, Lung Cancer Symptom Scale; LDH, lactate dehydrogenase; Mg, magnesium, MRI, magnetic resonance imaging; Na, sodium; TSH, thyroid stimulating hormone.

5.1.1 Retesting During Screening or Lead-in Period

Retesting of laboratory parameters and/or other assessments within any single Screening or Lead-in period will be permitted (in addition to any parameters that require a confirmatory value).

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

Laboratory parameters and/or assessments that are included in Table 5.1-1 may be repeated in an effort to find all possible well-qualified subjects. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

5.2 Study Materials

The following materials will be provided to all investigational sites:

- NCI CTCAE version 4
- Nivolumab Investigator Brochure
- Ipilimumab Investigator Brochure
- Pharmacy Binder

[redacted]

- Site manual for operation of interactive web-based response system, including enrollment/randomization worksheets
- Manual for entry of local laboratory data
- Pregnancy Surveillance Forms
- RECIST 1.1 pocket guide
- CA209722 study Imaging Manual
- EuroPRO Group's EQ-5D-3L questionnaires and Lung Cancer Symptom Score

5.3 Safety Assessments

At screening, a medical history will be obtained to capture relevant underlying conditions. The screening examinations should include weight, height, ECOG Performance Status, blood pressure (BP), heart rate (HR), and temperature should be performed within 14 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 within 14 days prior to the first dose through the study treatment period (see Section 5.1).

Screening local laboratory assessments should be done within 14 days prior to first dose and are to include: CBC w/differential, chemistry panel including albumin, LDH, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, phosphate, glucose, amylase, and lipase, and thyroid panel including TSH, free T4, and free T3.

The following screening local laboratory assessments should be done within 28 days prior to randomization: hepatitis B and C testing (HBsAg, HBcAb with reflex HBV DNA, and HCV RNA, and with reflex HCV Ab.

Screening pregnancy test for WOCBP (done locally) must be performed within 24 hours prior to initial administration of study drug.

While on-study the following local laboratory assessments are to be done within 3 days prior to each dose: CBC with differential, albumin, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, phosphate, LDH, glucose, amylase, and lipase. Thyroid function testing is to be done every 6 weeks for Arms A and B.

On-treatment pregnancy tests should be performed as per the Table 5.1-2.

Subjects will be evaluated for safety if they have received any study drug. Toxicity assessments will be continuous during the treatment phase. During the safety follow-up phase (Table 5.1-3), toxicity assessments should be done in person. Once subjects reach the survival follow-up phase, either in person or documented telephone calls to assess the subject's status are acceptable. Adverse events and laboratory values will be graded according to the NCI-CTCAE version 4.

The start and stop of the study therapy infusion and any interruptions or infusion rate reductions should be documented.

Physical examinations are to be performed as clinically indicated. 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.

On-study weight, ECOG PS, and vital signs should be assessed at each on-study visit prior to dosing. Vital signs should also be taken as per institutional standard of care prior to, during, and after infusions.

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.

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. An algorithm for the management of suspected pulmonary toxicity can be found in the nivolumab Investigator's Brochure and in Appendix 2.

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.

5.3.1 Imaging Assessment for the Study

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.

5.3.2 ECOG Performance Status

Eastern Cooperative Oncology Group (ECOG) Performance Status will be evaluated and documented at Screening and within 3 days prior to each dosing visit as outlined in Section 5.1. See **Appendix 3** for description of ECOG status.

5.3.3 Thyroid Function Testing (Arms A and B only)

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.

Management algorithms for suspected endocrinopathy adverse events (including abnormal thyroid function) can be found in the nivolumab Investigator Brochure and Appendix 2.

5.3.3.1 Electrocardiogram (ECG)

All subjects who have met the eligibility criteria are required to have a 12-lead ECG performed during Screening. If clinically indicated, additional ECGs may be obtained during the study.

5.4 Efficacy Assessments

Study evaluations (tumor assessments) will take place in accordance with the tables in Section 5.1. Images will be submitted to an imaging vendor for central review. Sites will be trained prior to scanning the first study subject. Image acquisition guidelines and submission process will be outlined in the CA209722 study Imaging Manual to be provided by the imaging vendor. Contrast enhanced CT with contrast or contrast enhanced MRI are 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 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.

Use of CT component of a PET/CT scanner: Combined modality scanning such as with FDG-PET/CT is increasingly used in clinical care, and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change rather quickly with time. At present, low dose or attenuation correction CT portions of a combined FDG-PET/CT are of limited use in anatomically-based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically-based RECIST measurements. However, if a site can document that the CT performed as part of a FDG-PET/CT is of identical diagnostic quality to a diagnostic CT (with contrast) then the CT

portion of the FDG-PET/CT can be used for RECIST 1.1 measurements. Note, however, that the FDG-PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

MRI of brain is preferred at screening in order to stratify patients based on the presence or absence of brain metastases. A CT with contrast is acceptable if MRI is not available.

Bone scan or PET scan is not adequate for assessment of RECIST 1.1 response in target lesions. 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.

Screening assessments are to be performed within 28 days prior to randomization. In addition to the chest, abdomen, pelvis, and brain (to identify subjects with brain metastases), all known sites of disease should be assessed at baseline. Subsequent assessments should include chest, abdomen, pelvis, and all known sites of disease using the same imaging method and technique as was used at baseline.

Radiographic tumor response will be assessed starting at Week 7 (6 weeks after first dose ± 7 days), then every 6 weeks (± 7 days) until Week 49 and every 12 weeks (± 7 days) thereafter, until disease progression is documented, treatment is discontinued (if still receiving treatment beyond disease progression) or the start of any subsequent anticancer therapy, whichever occurs later. Subjects with a current or past brain metastasis may have surveillance MRI or CT with contrast approximately every 12 weeks from the date of first dose, or sooner if clinically indicated.

Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible. Change in tumor measurements and tumor response will be assessed by the Investigator using the RECIST 1.1 criteria Appendix 4.

Tumor assessments should be submitted to the third-party radiology vendor as they are performed on an ongoing basis. At the time of investigator-assessed disease progression, the site must request an Independent Review of Progression from the third-party radiology vendor, as specified in Section 7.

Subjects whose disease progression is not confirmed by the blinded, independent radiologist will be required to continue tumor assessments (if clinically feasible) according to the protocol-specified schedule. Subsequent tumor assessments must be submitted to the third-party radiology vendor for review by the blinded, independent radiologists and may be discontinued when the investigator and independent radiologists both assess the subject to have met RECIST 1.1 criteria for progression.

In addition, subjects receiving nivolumab and/or ipilimumab treatment beyond progression must continue tumor assessments until such treatment has been discontinued.

If clinically acceptable, subsequent therapy should begin only after RECIST 1.1 progression has been assessed by central review upon Independent Review of Progression. Subjects who start palliative local therapy or subsequent therapy without prior assessment of RECIST 1.1 progression

by central review, the Independent Review of Progression must continue tumor assessments (if clinically feasible) according to the protocol-specified schedule and submit them to the third-party radiology vendor. When RECIST 1.1 progression is assessed by the investigator (whether assessed before or after the start of palliative local therapy or subsequent therapy), the central Independent Review of Progression must be requested. Tumor assessments may be discontinued when the independent radiologist assesses the subject to have met RECIST 1.1 criteria for progression

5.4.1 Primary Efficacy Assessment

The primary endpoint is PFS (based on BICR assessment) in all randomized subjects.

5.4.2 Secondary Efficacy Assessment

The secondary efficacy endpoints of the study are OS, ORR based on BICR assessment, DOR based on BIR, and 9-month and 12-month PFS based on BIR in all randomized subjects. See Section 8.3.2 for the definition of OS and ORR. All randomized subjects will be monitored by radiographic assessment, starting at Week 7 (± 7 days), then every 6 weeks (± 7 days) until Week 49 and every 12 weeks (± 7 days) thereafter, to determine changes in tumor size. RECIST 1.1 criteria will be used for the assessment. For details regarding response criteria using RECIST 1.1 refer to Appendix 4.

Every effort will be made to collect survival data on all subjects including subjects withdrawn from treatment for any reason, who are eligible to participate in the study and who have not withdrawn consent for survival data collection. If the death of a subject is not reported, all dates in this study representing a date of subject contact will be used in determination of the subject's last known date alive.

[redacted]

5.6 Biomarker Assessments

5.6.1 Tumor Tissue Specimens

Archival (or fresh) FFPE tumor tissue collected within 6 months must be sent to a third-party laboratory for determination of PD-L1 status using the analytically validated IHC assay. If an archival tissue was obtained more than 6 months prior to the study treatment and fresh biopsy cannot be performed, approval of Medical Monitor is required, Stained tissue samples will be assessed by a pathologist at a central lab identified by the Sponsor and scored as PD-L1 expressing if membrane staining is observed in ≥ 1% tumor cells among a minimum of 100 evaluable tumor cells. A re-biopsy at Week 7 and at disease progression is highly recommended. This on-treatment collection will provide valuable information on pharmacodynamic changes in both immune-related and other biomarkers within the tumor and tumor microenvironment which may be associated with treatment outcomes. Week 7 was chosen to ensure that subjects treated with nivolumab and ipilimumab combination receive at least 1 full cycle of treatment. An additional optional tumor biopsy is also highly recommended at the time of progressive disease; such samples may provide valuable insight into the changes that occur in the tumor and tumor microenvironment at the time of acquired resistance.

[redacted]

[redacted]

EGFR Mutation Testing

As part of study inclusion criteria, subjects must have no evidence of exon 20 T790M mutation detected by tumor biopsy or cfDNA analysis obtained at progression on prior EGFR TKI therapy. Confirmation of T790M testing by tumor tissue will be conducted centrally or locally using the cobas®EGFR Mutation Test v2 (US-IVD). As an additional exploratory analysis, plasma will be collected as baseline and on-treatment and may be evaluated using the cobas®EGFR Mutation Test. EGFR mutation results from plasma will be compared to those obtained from tumor material.

[redacted]

[redacted]

[redacted]

5.7 Outcomes Research Assessments

The evaluation of health-related quality of life is an increasingly important aspect of a clinical efficacy. Such data provides an understanding of the impact of treatment from the subjects' perspective and offers insights into the patient experience that may not be captured through physician reporting. Generic health-related quality of life scales additionally provide data necessary in calculating utility values for health economic models. The EQ-5D-3L will be collected in order to assess the impact of study treatment on generic health-related quality of life, which will also be used in populating health economic models most notably, a cost effectiveness analysis.

The EQ-5D-3L will be used to assess the subject's overall health status. EQ-5D-3L essentially has 2 components: the EQ-5D-3L descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D-3L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, severe problems. The EQ-5D-3L problem has been mapped into EQ-5D-3L utility index using the problem levels from the 5 health dimensions. The EQ VAS records the subject's self-rated health state on a 100-point vertical, visual analogue scale (0 = worst imaginable health state, 100 = best imaginable health state).

The Lung Cancer Symptom Scale (LCSS) will be collected to assess the impact of study treatment on patient reported disease-related symptoms.

The Lung Cancer Symptom Scale is a validated instrument designed to assess the impact of treatment on disease-related symptoms. It consists of 6 symptom specific questions related to dyspnea, cough, fatigue, pain, hemoptysis, and anorexia plus 3 summary items: symptom distress, interference with activity, and global health-related quality of life (HRQoL). The degree of impairment is recorded on a 100 mm visual analogue scale with scores from 0 to 100 with zero representing the best score.

5.8 Other Assessments

Not applicable.

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.)

Sponsor or designee will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320.

6.1 Serious Adverse Events

A S***erious 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 drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 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 drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE (see Section 6.1.1 for reporting details).

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1, 5.6.2, and 5.6.3 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. For subjects randomized to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of randomization. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

The investigator must 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 must 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 must 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 Sponsor 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. In the event the electronic system is unavailable for transmission, paper forms must be used and submitted immediately. 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 must 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, the SAE report must be updated and submitted within 24 hours to Sponsor or designee using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

BMS will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320. A SUSAR (Suspected, Unexpected Serious Adverse Reaction) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

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

The collection of nonserious AE information should begin at initiation of study drug. 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.

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.

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.

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 subject's case report form.

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form electronic) as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

- 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).

6.4 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 Sponsor or 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). Please call the Sponsor or designee within 24 hours of awareness of the pregnancy.

The investigator must immediately notify the Sponsor or designee of this event and complete and forward a Pregnancy Surveillance Form to Sponsor 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 Sponsor or designee. In order for BMS to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 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.).

6.6 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:

- AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)
  AND
- Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),
  AND
- 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.

6.7 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.

6.7.1 Adverse Events of Interest

Definition of immune-mediated adverse events (IMAEs)

Immune-mediated AEs are specific events (that include pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, and endocrine [adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis]) for which subjects received immunosuppressive medication for treatment of the event, with the exception of endocrine events (hypothyroidism/thyroiditis, hyperthyroidism, hypophysitis, diabetes mellitus, adrenal insufficiency), which are included regardless of treatment since these events are often managed without immunosuppression.

IMAEs include events, regardless of causality, occurring within 100 days of the last dose. IMAEs 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 are included regardless of treatment since these events are often managed without immunosuppression.

Table 6.7.1-1 below provides a summary of the IMAEs category and their respective preferred terms.

Table 6.7.1-1: Preferred Terms Included in Analysis of IMAEs to Support Warnings and Precautions

IMAE Category	PTs 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 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 maculopapular

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

When required, adjudicated events will be submitted to the DMC and Health Authorities for review on a specified timeframe in accordance with the adjudication documentation.

A Data Monitoring Committee (DMC) will be utilized to provide general oversight and safety considerations for this study, CA209722. The DMC will provide advice to the Sponsor regarding actions the committee deems necessary for the continuing protection of subjects enrolled in this study. The DMC will be charged with assessing such actions in light of an acceptable risk/benefit profile for nivolumab. The DMC will act in an advisory capacity to BMS and will monitor subject safety data for the study.

The DMC will be advisor to the clinical study leadership team. The clinical study leadership 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 amendments to the protocol or changes to the study conduct are required.

The DMC will conduct the first safety assessment for Arms A and B after the first 15 subjects are treated in each arm and followed for at least 3 months. A safety assessment will also be conducted after the first 15 patients from Asian sites are treated in each arm and followed for at least 3 months. Additional safety assessments for Arms A and B will be conducted approximately every 6 months.

Details of the DMC responsibilities and procedures will be specified in the DMC charter.

Independent Review of Progression at the Time of Investigator-assessed Progression

At the time of investigator-assessed initial radiographic progression per RECIST 1.1 in any given subject, the site must request the blinded Independent Review of Progression from the third-party radiology vendor.

Tumor assessments for each subject should be submitted to the radiology vendor as they are performed on an ongoing basis. The blinded, independent radiologists will review all available tumor assessments for that given subject and determine if RECIST 1.1 criteria for progression have been met. The independent assessment of whether or not the given subject met RECIST 1.1 criteria for progression will be provided to the site. Subjects whose disease progression is not confirmed centrally will be required to continue tumor assessments (if clinically feasible) according to the protocol-specified schedule. Subsequent tumor assessments must be submitted to the third-party radiology vendor for subsequent review and may be discontinued when the investigator and independent radiologists both assess the subject to have met RECIST 1.1 criteria for progression or the start of any subsequent anti-therapy, whichever occurs first.

The Blinded Independent Central Review (BICR) will review tumor images in all randomized subjects to determine RECIST 1.1 response for the analyses of PFS, ORR, and DOR. Details of the BICR responsibilities and procedures will be specified in the BICR charter.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

The sample size of the study accounts for: the primary objective comparison of PFS assessed by BICR between nivolumab plus pemetrexed/platinum vs pemetrexed plus platinum.

No interim analysis for PFS is planned. Piece-wise exponential distributions of PFS are assumed in the pemetrexed plus platinum arm with median PFS of 4.5 months and in the nivolumab plus pemetrexed/platinum arm with median PFS of 6.5 months. Approximately 233 PFS events observed among the 270 randomized subjects (135 per Arms A and C) provides an average of 83% power to detect an average HR of 0.692 with type 1 error of 0.05.

Before revised protocol 04, subjects were randomized between 3 arms in a 1:1:1 ratio. Revised protocol 04 stops enrollment in Arm B (nivolumab plus ipilimumab) but continues to randomize eligible subjects into either nivolumab plus platinum doublet chemotherapy arm (Arm A) or platinum doublet chemotherapy arm (Arm C) in 1:1 ratio. Approximately 270 subjects will be randomized between Arms A and C. Subjects already randomized in Arm B of nivolumab plus ipilimumab may remain on treatment, at the discretion of the investigator.

The PFS analysis will be conducted when the following conditions have been met: 233 PFS events have been reported and/or the minimum follow up is at least 6 months.

Table 8.1-1 summarizes the key parameters of the sample size justification for PFS comparison.

Table 8.1-1: Sample Size Justification for PFS Comparison

Primary analysis comparison population	Arm A and Arm C
Endpoint	**PFS**
Average Power	83%
Alpha	0.05
Hypothesized Median PFS Arm C vs Arm A (months)	4.5 vs 6.5
Hypothesized Hazard ratio	0.692 (HR=1 from 0-2 months, and 0.569 from month 2 on)
Sample size for Arm A and Arm C comparison	270
Expected number of events	233

If superiority in PFS is demonstrated for nivolumab plus platinum doublet chemotherapy arm (Arm A) vs platinum doublet chemotherapy arm (Arm C), the key secondary endpoint OS will be tested at alpha 0.05. Assuming a hazard ratio of 0.72 (median 18 vs 25 months), it is estimated that there will be approximately 133 total deaths at the time of the PFS analysis, which would provide approximately 10% power for rejecting a null hypothesis of no difference at the 0.05 type I error level; if all subjects are followed to death, the power increases to 33%.

The above sample size calculation is based on simulations run on EAST 6.4.1.

8.2 Populations for Analyses

- **All enrolled subjects**: All subjects who signed an informed consent form and were registered into the IWRS
- **All randomized subjects**: All subjects who were randomized to any treatment group in the study
- **All treated subjects**: All subjects who received at least 1 dose of study treatment
- **Response evaluable subjects**: Randomized subjects whose change in the sum of diameters of target lesions was assessed (eg, target lesion measurements were made at baseline and at least one on-study tumor assessment)

8.3 Endpoints

8.3.1 Primary Endpoint(s)

PFS assessment by BICR is the primary endpoint for this study. PFS is defined as the time between the date of randomization and the first date of documented progression, as determined by BICR, or death, whichever occurs first. Subjects who die without a reported 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 their date of randomization. Subjects who started non-study anti-cancer therapy without a prior reported progression will be censored on the date of their last evaluable tumor assessment prior to the initiation of subsequent anti-cancer therapy.

8.3.2 Secondary Endpoint(s)

- OS is the key secondary endpoint. OS is defined as the time between the date of randomization and the date of death. OS will be censored on the last date a subject was known to be alive.
- ORR per RECIST 1.1 by BICR is a secondary endpoint. The ORR is defined as the number of subjects with a BOR of CR or PR divided by the number of randomized subjects for each treatment group. The BOR is defined as the best response designation, as determined by BICR, recorded between the date of randomization and the date of objectively documented progression per RECIST 1.1 or the date of subsequent anti-cancer therapy, whichever occurs first. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR assessment.
- The other secondary endpoints include DOR by BICR and the 9-month and 12-month PFS rates by BICR. DOR is defined as the time between the date of first confirmed response to the date of the first documented tumor progression (per RECIST 1.1) by BICR or death. Subjects who neither progress nor die will be censored on the date of their last assessment.

8.3.3 Exploratory Endpoint(s)

- The safety and tolerability objective will be measured by the incidence of adverse events, serious adverse events, deaths, and laboratory abnormalities
- PFS, OS, and ORR by PD-L1 status (≥ 1% and < 1%/not evaluable/indeterminate) (source: clinical database)

[redacted]

- To assess health-related quality of life using the EQ-5D-3L and LCSS
- To evaluate ORR, PFS and OS in the subjects treated with nivolumab plus ipilimumab (Arm B)
- To evaluate PFS after next line of treatment (PFS2)

[redacted]

8.4 Analyses

Analyses of PFS will be conducted first followed by analysis of OS.

8.4.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized in all randomized subjects by treatment group, as randomized, using descriptive statistics.

8.4.2 Efficacy Analyses

Analysis of PFS will be conducted first followed by analysis of OS in hierarchical order. Primary PFS analysis will be conducted using a 2-sided log-rank test stratified by PD-L1 status (≥1% or <1%/not evaluable/indeterminate), by presence or absence of brain metastases, by smoking history (current/former smokers or never smokers), and by prior use of osimertinib (yes or no) in randomized subjects to compare Arm A to Arm C. HR and corresponding 2-sided 95% CI will be estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by the above stratification factors. PFS curves, PFS medians with 95% CIs, and PFS rates at 6, 9 and 12 months with 95% CIs will be estimated using Kaplan-Meier methodology.

The secondary endpoint of OS will be tested if PFS superiority is demonstrated for Arm A versus Arm C. The OS hypothesis testing will be conducted using a 2-sided log-rank test stratified by PD-L1 status, by presence or absence of brain metastases, smoking history, and by prior use of osimertinib in all randomized subjects to compare Arm A to Arm C. The HR and corresponding 2-sided 95% CI will be estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by the stratification factors. OS curves, OS medians with 95% CIs, and OS rates at 9, 12 and 24 months with 95% CIs will be estimated using Kaplan-Meier methodology.

ORR analyses will be conducted at the time for PFS analysis. An estimate of the difference in ORRs and corresponding 95% CI will be calculated using Cochran-Mantel-Haenszel (CMH) methodology and stratified by PD-L1 status, by presence or absence of brain metastases, smoking history, and by prior use of osimertinib to compare Arm A to Arm C. Additionally, ORRs and their corresponding 95% exact CIs will be calculated using the Clopper-Pearson method for each arm. DOR in each treatment arm will be estimated using KM product-limit method for subjects who achieved PR or CR. Median values along with 2-sided 95% CI will be calculated.

PFS, OS, and ORR will be analyzed within each PD-L1 status subgroup (≥1% and < 1%/not evaluable/indeterminate) (source: clinical database) by applying unstratified model. These analyses by PD-L1 status will be descriptive and not adjusted for multiplicity.

Descriptive analyses for PFS, OS, and ORR will be provided for Arm B.

8.4.3 Safety Analyses

Safety analyses will be performed in all treated subjects. Descriptive statistics of safety will be presented using NCI CTCAE version 4. All on-study AEs, drug-related, AEs, SAEs and drug-related SAEs will be tabulated using worst grade per NCI CTCAE v 4 criteria by system organ class and MedDRA preferred term. On-study laboratory parameters including hematology, chemistry, liver function, thyroid function, and renal function will be summarized using worst grade per NCI CTCAE v 4 criteria.

8.4.6 Outcomes Research Analyses

Outcome research analysis will be performed based on all randomized subjects. LCSS and EQ-5D-3L questionnaire complete rates, defined as the proportion of questionnaires actually received out of the expected number (ie, the number of subjects still on treatment in follow-up), will be calculated and summarized at each assessment point (each on-treatment assessment and assessments at Follow-up Visits 1 and 2).

The rate of disease-related symptom improvement as measured by the LCSS average symptom burden index (ASBI) at 12 and 24 weeks after the first dose (at Weeks 13 and 25 assessments) and its corresponding 95% exact CIs will also be calculated by Clopper-Pearson method for each randomized arms (all randomized patients). In a similar fashion, the rate of disease-related symptoms stability (no improvement or worsening) and rate of symptom worsening at 12 and 24 weeks after the first dose (at Weeks 13 and 25 assessments) will be calculated. For the each of these time periods (Weeks 13 and 25), an odds ratio across study arms (and its 95% CI) of the proportion of patients at each level (improvement, stability, worsening) will be calculated, with Arm A being compared to Arm C. In addition, the time to first symptom deterioration (TTSD) as measured by the ASBI of the LCSS will be evaluated, with the TTSD in Arm A to be compared to Arm C. The LCSS ASBI score and its change from baseline will be summarized using descriptive statistics (N, mean, median, SD, and 95% CI) at each assessment point by treatment group as randomized.

The level of subject's overall health state, as expressed by the visual analog scale (EQ-VAS) and the EQ-5D-3L index, as well as change from baseline will be evaluated at each assessment time

point and will be summarized using descriptive statistics (N, mean, median, SD, and 95% CI) by treatment group, as randomized.

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

8.4.7 Other Analyses

PFS2 is defined as the time from randomization to the date of investigator-defined documented disease progression after next line of treatment or death due to any cause, whichever comes first. Clinical deterioration will not be considered as progression. A participant who neither progresses after next line of treatment nor dies will be censored on the date of his/her last adequate tumor assessment or last follow-up for progression/subsequent therapy. A participant who does not have any post-baseline tumor assessments and who has not died will be censored on the date at which he/she was randomized.

[redacted]

8.5 Interim Analyses

No interim analyses are planned.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if applicable, also by local health authority) 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 relevant approval/favorable opinion(s), the deviation or change will be submitted as soon as possible to:

- IRB/IEC
- Regulatory Authority(ies), if applicable by local regulations per national requirements)

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and if applicable, also by local health authority, 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 or designee 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.

In addition, the study may be evaluated by BMS or designee 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 or designee.

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.

9.2 Records

9.2.1 Records Retention

The investigator (or head of the study site in Japan) 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 or designee, whichever is longer. The investigator (or head of the study site in Japan) must contact BMS or designee prior to destroying any records associated with the study.

BMS or designee will notify the investigator (or head of the study site in Japan) 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, study site, IRB). Notice of such transfer will be given in writing to BMS or designee.

9.2.2 Study Drug Records

Records for IP (whether supplied by BMS, its vendors, or the site) must substantiate IP integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

If...	Then...
Supplied by BMS (or its vendors):	• 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 • nonstudy disposition (e.g., lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • 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.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study drug integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy. These records should include: • label identification number or batch number • amount dispensed to and returned by each subject, including unique subject identifiers • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

BMS or designee 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 Sponsor or designee 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 electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by Sponsor of designee.

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, 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. Subinvestigators in Japan may not be delegated the CRF approval task. 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 Sponsor or designee training requirements and must only access the BMS electronic data capture tool using the unique user account provided by Sponsor or designee. 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:

- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to BMS or designee. 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 or designee 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	Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. 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. Women must continue to have pregnancy tests. Acceptable alternate methods of highly or less effective contraception's must be discussed in the event that the subject chooses to forego complete abstinence.

11 LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
ASBI	Average symptom burden index
AST	aspartate aminotransferase
AT	aminotransaminases
BID, bid	bis in die, twice daily
BICR	Blinded independent central review
BMI	body mass index
BMS	Bristol-Myers Squibb
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CNS	Central nervous system
CRF	Case Report Form, paper or electronic
DOR	duration of response
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEG	electroencephalogram
Eg	exempli gratia (for example)
EGFR	epidermal growth factor
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
g	Gram
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus

Term	Definition
HCV	hepatitis C virus
HIV	Human Immunodeficiency Virus
HR	heart rate
HRT	hormone replacement therapy
IC	Informed consent
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
IRB	Institutional Review Board
IV	intravenous
IWRS	Interactive web response system
LCSS	Lung Cancer Symptom Scale
LDH	lactate dehydrogenase
mg	milligram
min	minute
mL	milliliter
NIMP	non-investigational medicinal products
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	Progressive disease
PFS	progression-free survival
PFS2	progression-free survival after next line of therapy
PK	pharmacokinetics
RBC	red blood cell
SAE	serious adverse event
SD	Stable disease

Term	Definition
SOC	Standard of care
TKI	tyrosine kinase inhibitor
TTSD	Time to first symptom deterioration
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
1L	first line
2L	second line

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APPENDIX 1 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state 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 > 40 mIU/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 judgement in checking serum FSH levels.

- 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. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal.

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 5 months after the end of study treatment, plus 30 days

Local laws and regulations may require use of alternative and/or additional contraception methods.

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation (These methods of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited)[b] – oral (birth control pills) – intravaginal (vaginal birth control suppositories, rings, creams, gels) – transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited)[b] • Intrauterine device (IUD)[c] • Intrauterine hormone-releasing system (IUS) (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited) [b,c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence

NOTES:

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.

[c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Less Than Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of >1% per year when used consistently and correctly.*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal Sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited)
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal(coitus interruptus). • Spermicide only • Lactation amenorrhea method (LAM)

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILD BEARING POTENTIAL.

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP; even if the participants have undergone a successful vasectomy or if their partner is already pregnant or breastfeeding. Males should continue to use a condom while on study plus 5 half-lives of study treatments plus 90 days (duration of sperm turnover). Withdrawal (coitus interruptus) and/or the use of a spermicide without a condom are not acceptable methods of contraception or fetal protection.

- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 8 months days/weeks after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from sexual activity or use a male condom during any sexual activity (eg, vaginal, anal, oral) even if the participants have undergone a successful vasectomy, while on study plus 5 half-lives of study treatments plus 90 days (duration of sperm turnover). Withdrawal (coitus interruptus) and/or the use of a spermicide without a condom are not acceptable methods of contraception or fetal protection.
- Refrain from donating sperm for the duration of the study treatment and for 8 months after the end of treatment.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 6.4 and the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting

APPENDIX 2 MANAGEMENT ALGORITHMS FOR IMMUNO-ONCOLOGY AGENTS

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

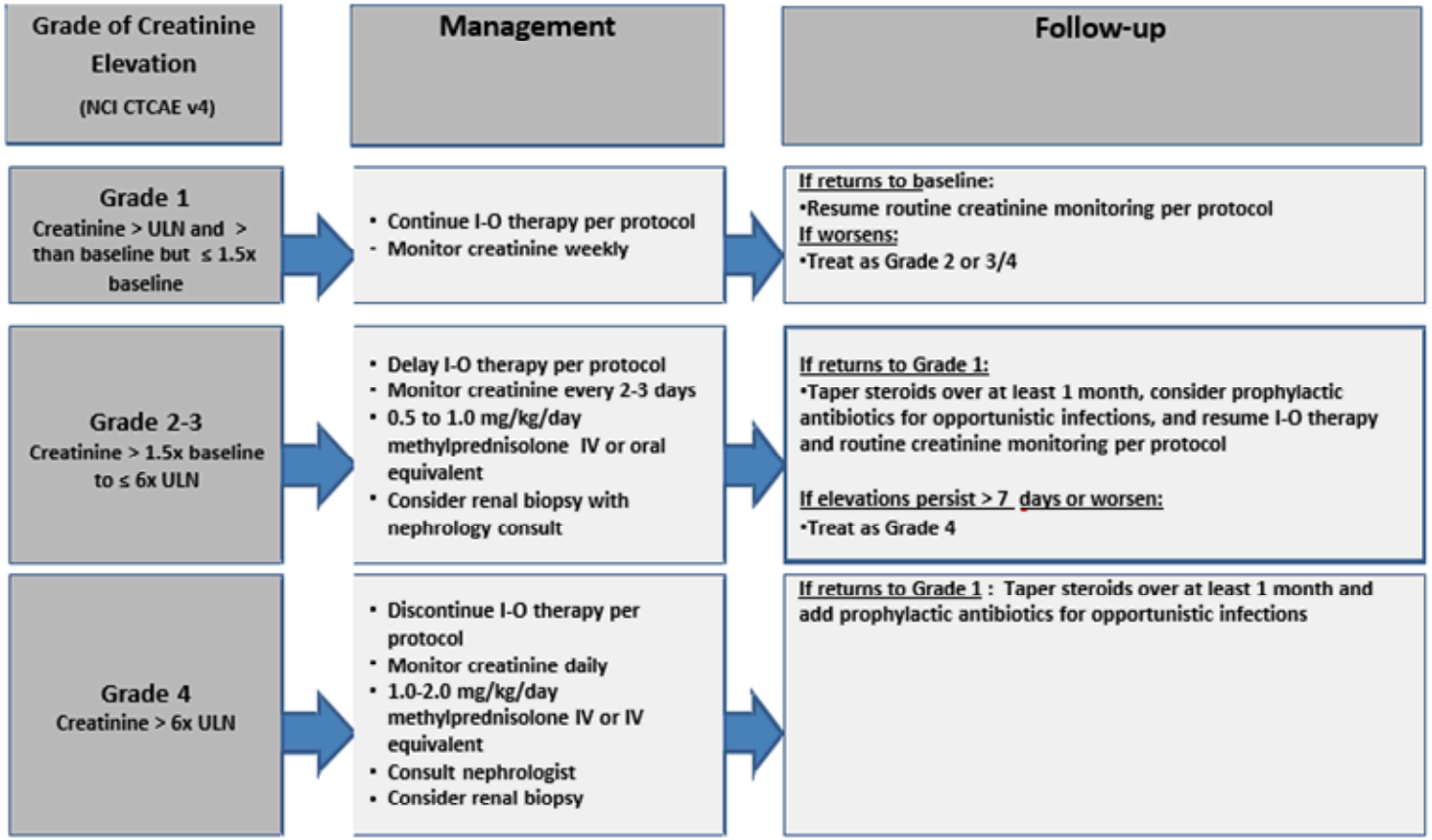
Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

25-Jun-2019

Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

25-Jun-2019

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

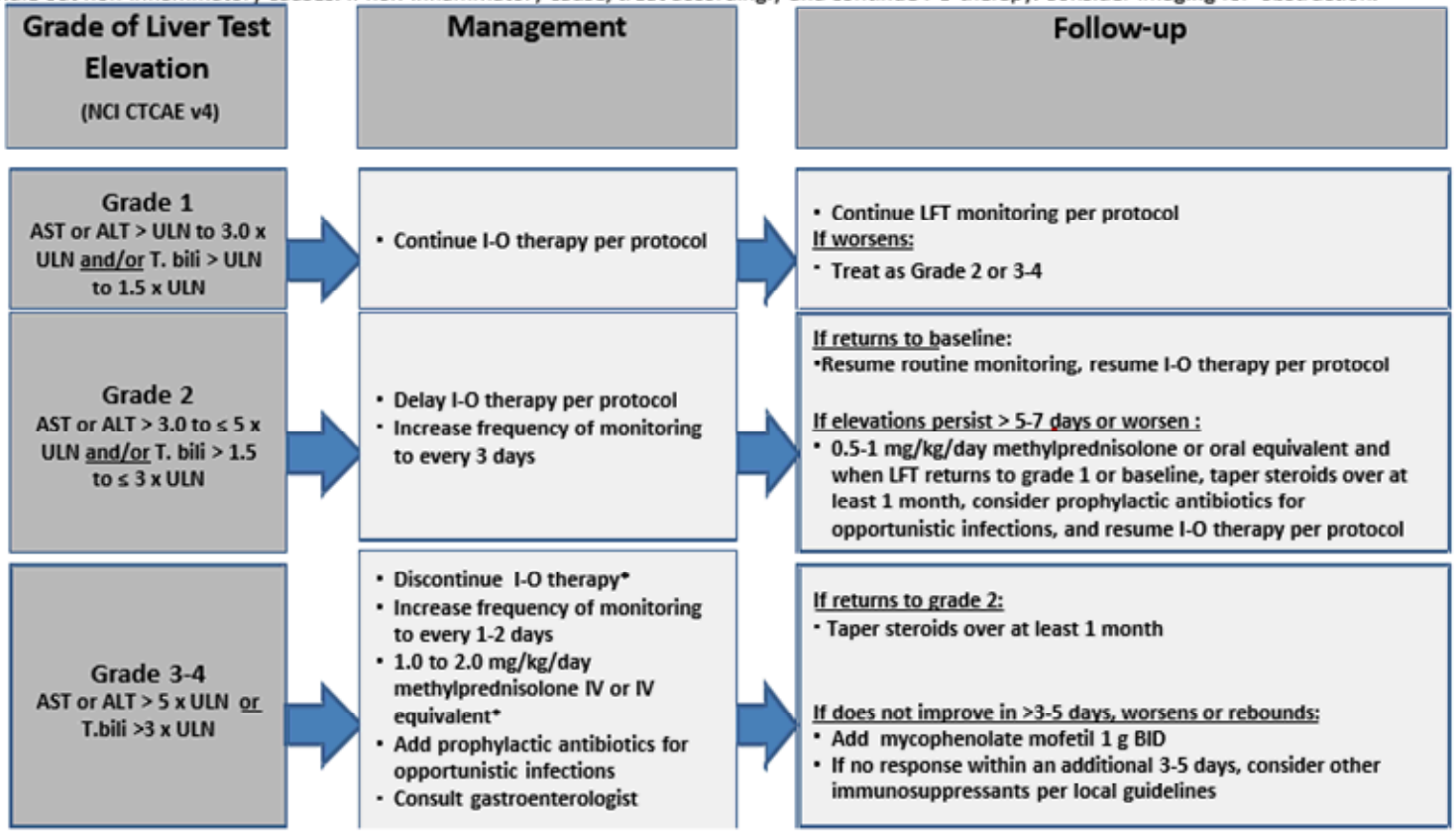
Grade of Pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and ID consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms	• Delay I-O therapy per protocol • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent • Consider bronchoscopy , lung biopsy	• Re-image every 1-3 days If improves: - When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics If not improving after 2 weeks or worsening: - Treat as Grade 3-4
Grade 3-4 Severe new symptoms; New/worsening hypoxia; Life-threatening	• Discontinue I-O therapy per protocol • Hospitalize • Pulmonary and ID consults • 2-4 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections - Consider bronchoscopy, lung biopsy	If improves to baseline: • Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: - Add additional immunosuppression

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids

25-Jun-2019

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.



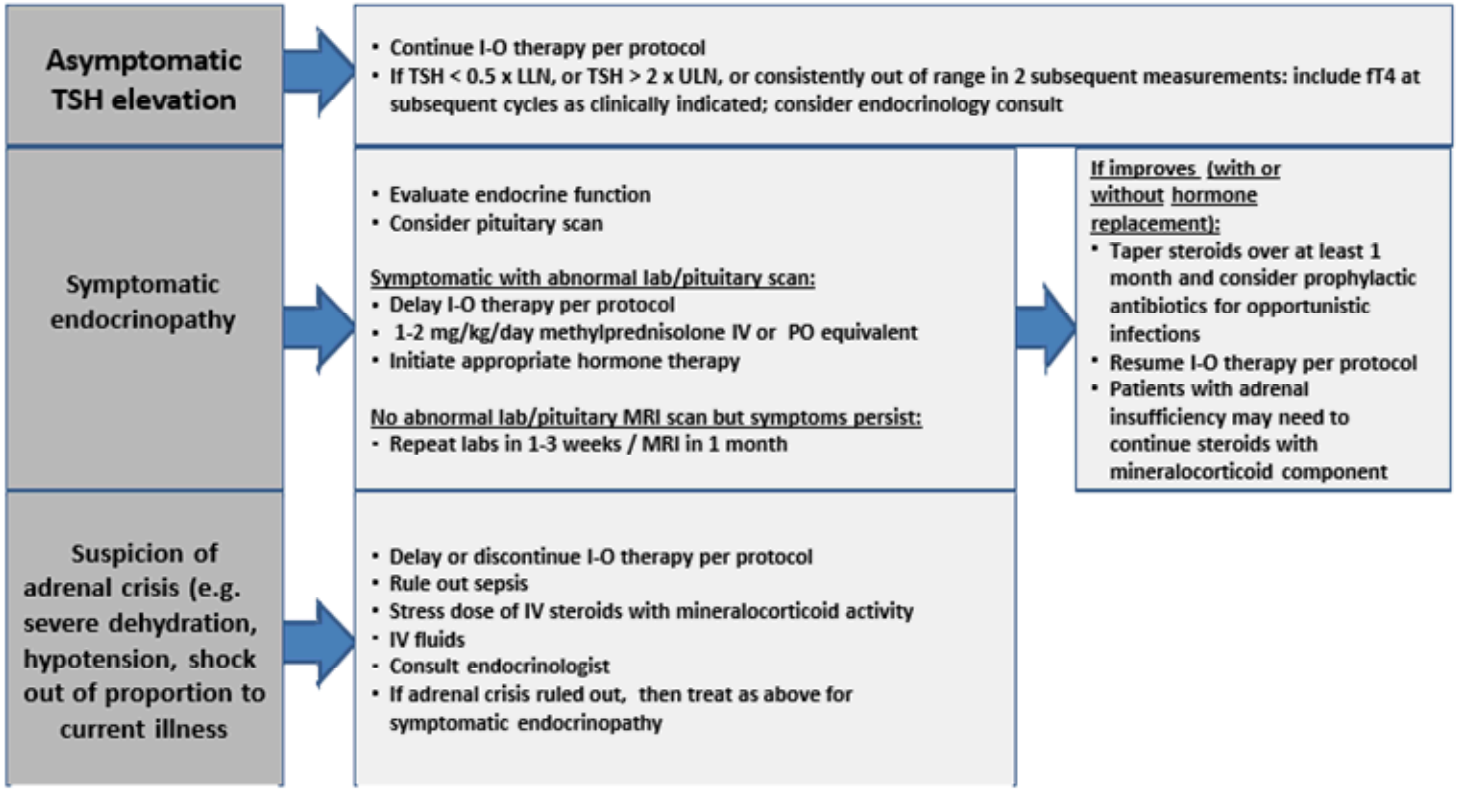
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

25-Jun-2019

Endocrinopathy Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.

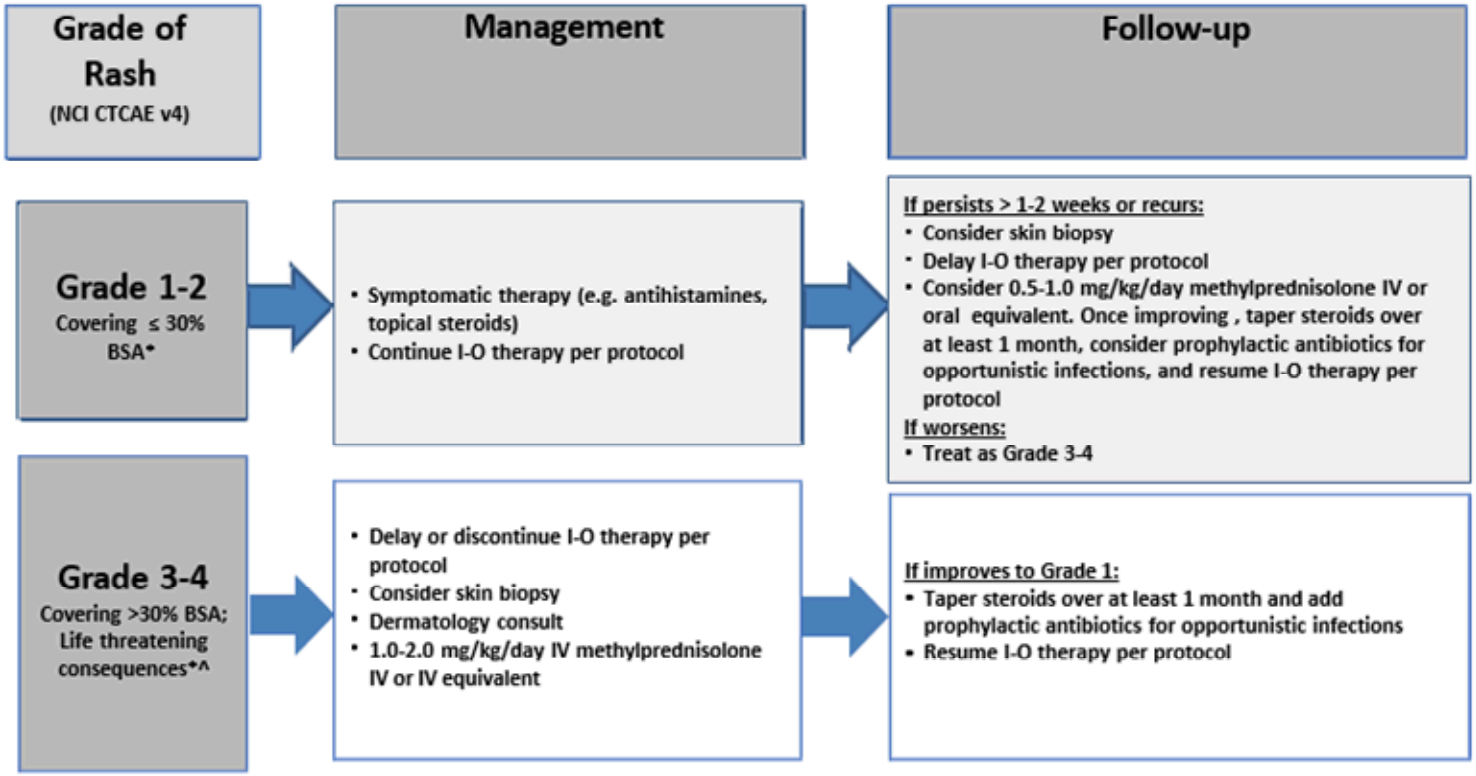


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

25-Jun-2019

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

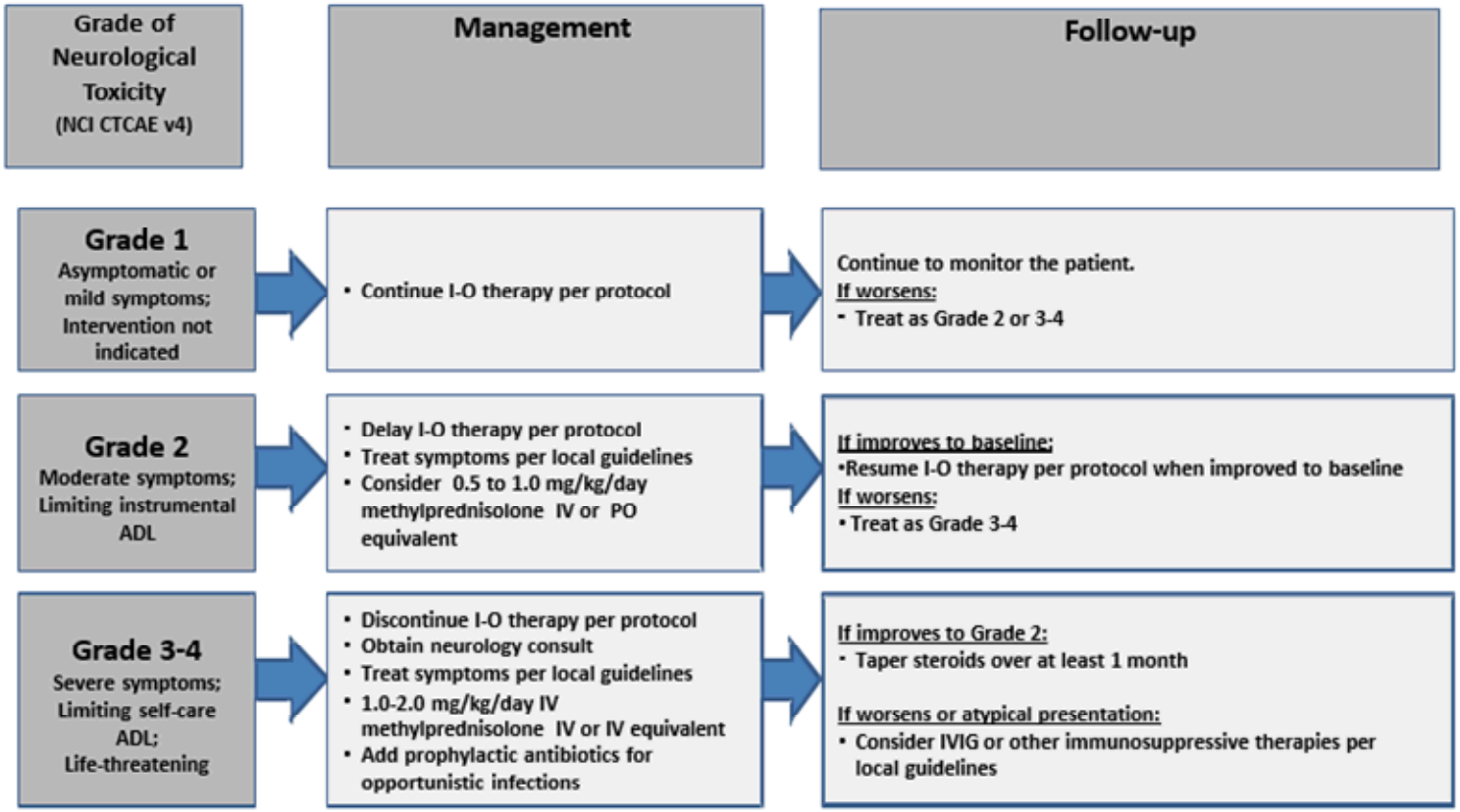
*Refer to NCI CTCAE v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

25-Jun-2019

Neurological Adverse Event Management Algorithm

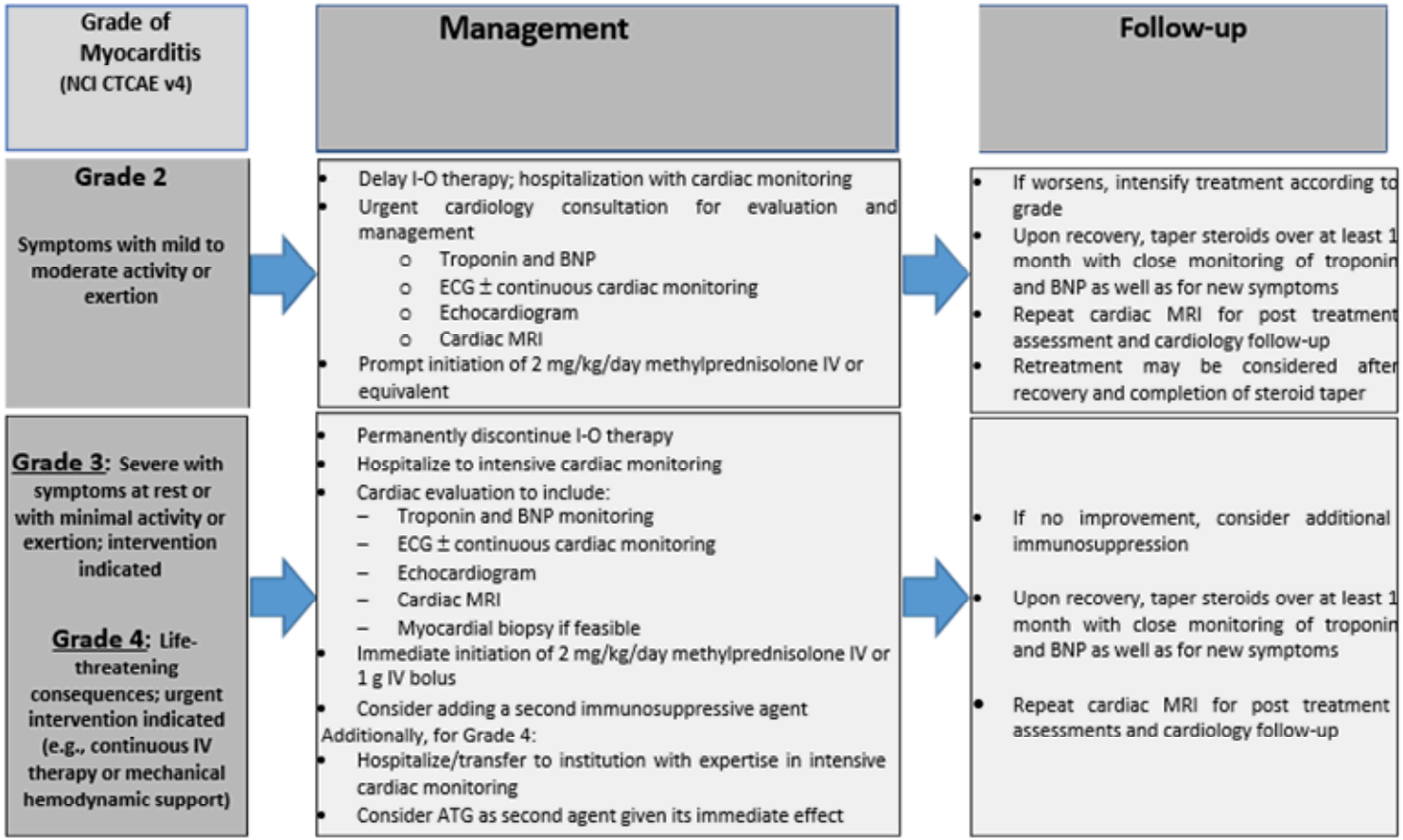
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

25-Jun-2019

Myocarditis Adverse Event Management Algorithm



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.

ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging

25-Jun-2019

APPENDIX 3 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

[a] Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, and Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649-655.

APPENDIX 4 RESPONSE CRITERIA (RECIST 1.1)

1 EVALUATION OF LESIONS

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

1.1 Measurable

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is 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).

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. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

1.2 Non-Measurable

All other lesions are considered non-measurable, including small lesions (longest diameter < 10mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly 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.

2 BASELINE DOCUMENTATION OF 'TARGET' AND 'NON-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 (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

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. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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 in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple nontarget 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 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 to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

3.1.1 Special Notes on the Assessment of Target Lesions

3.1.1.1 Lymph nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (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. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

3.1.1.2 Target lesions that become 'too small to measure'

While on study, 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). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. 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: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is 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). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

3.1.1.3 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 truly 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

This section provides the definitions of the criteria used to determine the tumor response for the group 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 (< 10mm 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 (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

3.2.1 Special Notes on Assessment of Progression of Non-Target Disease

The concept of progression of non-target disease requires additional explanation as follows:

3.2.1.1 When the patient also has measurable disease

In this setting, 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 (see examples in Appendix 2 and further details below). A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

3.2.1.2 When the patient has only non-measurable disease

This circumstance arises in some trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly 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. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

3.2.2 New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, 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 evidence of 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 truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan. 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.
2. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. 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 truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). 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.

3.3 Response Assessment

3.3.1 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement.

3.3.2 Time Point Response

It is assumed that at each protocol specified time point, a response assessment occurs. Table 3.3.2-1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore non-target) disease only, Table 3.3.2-2 is to be used.

Table 3.3.2-1: 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

Table 3.3.2-2: Time Point Response - Patients with Non-target Disease Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR = complete response, PD = progressive disease and NE = inevaluable		

[a] Non-CR/non-PD is preferred over SD for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

3.3.3 Best Overall Response

Best response determination of complete or partial response requires confirmation: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point

of ≥ 4 weeks later. In this circumstance, the best overall response can be interpreted as in Table 3.3.3-1.

Special note 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).

Table 3.3.3-1: Best Overall Response (Confirmation of CR&PR Required)

Overall Response First Time Point	Overall Response Subsequent Time Point	BEST Overall Response
CR	CR	CR
CR	PR	SD, PD OR PR[a]
CR	SD	SD provided minimum criteria for SD duration[b] met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration[b] met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration[b] met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration[b] met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration [b]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.

[b] Minimum criteria for SD duration is 6 weeks.

3.3.4 Confirmation Scans

Verification of Response: To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive repeat assessments that should be performed no less than 28 days after the criteria for response are first met. For this study, the next scheduled tumor assessment can meet this requirement.

Verification of Progression: Progression of disease should be verified in cases where progression is equivocal. If repeat scans confirm PD, then progression should be declared using the date of the initial scan. If repeat scans do not confirm PD, then the subject is considered to not have progressive disease.

APPENDIX 5 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for the Revised Protocol 05, 22-Mar-2019

The CA209722 revised protocol 05 updates the study title.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page Synopsis Section 1.5 Overall Risk/Benefit Section 3.1 Study Design and Duration	Updated study title to remove T790M negative requirement and include subjects who failed 2L TKI EGFR therapy.	Title was updated to align with updated study design in revised protocol 04. The T790M negative requirement was removed as subjects who progressed on osimertinib are allowed, regardless of T790M mutation status. In addition, subjects who failed 2L EGFR TKI are allowed

Overall Rationale for the Revised Protocol 04, 20-Nov-2018

The CA209722 revised protocol 04 reflects the current treatment landscape in patients with EGFR-mutated metastatic NSCLC. A recent meta-analysis of several clinical studies in advanced NSCLC patients with EGFR mutations in second line of therapy suggested a trend toward less clinical benefit from PD-(L)1 monotherapy when compared with chemotherapy (pooled HR, 1.11; 95%CI: 0.80, 1.53).[1] New body of evidence is accumulating to show that Tumor Mutational Burden (TMB) in EGFR-mutated NSCLC patients is significantly lower than that in EFGR wild-type NSCLC patients. [2] The recent data from CheckMate 227 indicated that NSCLC patients with low TMB are unlikely to derive PFS or ORR benefits from nivolumab and ipilimumab combination therapy when compared with chemotherapy, [3] suggesting that the combination of nivolumab and ipilimumab has a lower chance of success compared to chemotherapy containing arms. Thus, using nivolumab plus ipilimumab as one of the study arms has become potentially sub-optimal for patients who failed 1L or 2L TKIs moving forward. Therefore, the enrollment to nivolumab and ipilimumab combination arm (ie, Arm B) has stopped as of revised protocol 04. No safety concerns were identified among patients who received nivolumab and ipilimumab combination therapy in the study based on periodical DMC safety review.

Osimertinib has been the standard of care as a 2L treatment for the patients who failed the 1L first- and/or second-generation TKIs with T790M mutation, and previous study population included only patients who failed 1L first- and second-generation TKIs without T790M mutation. With recent approval of osimertinib[4, 5], a third generation TKI, in the first-line setting

and consequent limited treatment options post osimertinib, the revised protocol allows the enrollment of patients who failed osimertinib as 1L or 2L. Patients that fail osimertinib represent a high unmet need due to the lack of treatment options since resistance mechanisms have not be identified yet.

In addition, T790 mutation testing has been expanded to allow for local laboratory testing when using an approved assay. Other changes to stratification factors and eligibility were also made to the revised protocol.

Revisions apply to all future participants enrolled in the study, and where applicable, to all participants currently enrolled.

Summary of key changes of Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis Section 1. Introduction and Rationale Section 1.1.3 Rationale for Removing Combination of Nivolumab and Ipilimumab Arm Section 1.3.3 Exploratory Objectives Section 3.1 Study Design and Duration Figure 3.1-1 Study Design Schematic Section 8.3.3 Exploratory Endpoints Section 8.4.2 Efficacy Analyses	Arm B (nivolumab + ipilimumab) has stopped enrollment and subsequently, moved PFS, OS and ORR of nivolumab + ipilimumab vs chemotherapy to exploratory objectives	Emerging data suggest that the combination of nivolumab and ipilimumab has a lower chance of success compared to chemotherapy containing arms and becomes potentially sub-optimal treatment option for the target population
Synopsis Section 1. Introduction and Rationale Section 3.3.1 Inclusion Criteria Section 1.1.4 Rationale for Adding Subjects Previously Treated with	Allowed enrollment of subjects who were treated with 1L or 2L osimertinib regardless of T790M status	Osimertinib was approved as a 1L treatment for metastatic EGFR-mutated NSCLC regardless of T790M status in US, Europe and Japan, and is anticipated to be approved in other countries in the near future. The treatment option post osimertinib is very

Summary of key changes of Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Osimertinib Section 1.2 Research Hypothesis Section 1.3.1 Primary Objective		limited. Patients that fail osimertinib represent a high unmet need.
Synopsis Section 3.3.1 Inclusion Criteria Table 5.1-2 On-treatment Procedural Outline	Allowed randomization of subjects with asymptomatic CNS metastases and treatment of CNS metastases during the screening period.	Recent data suggest that the presence or absence of CNS metastases did not affect the clinical benefit of immunotherapy in advanced NSCLC patients. Allowing patients with CNS metastases to be treated during the screening period will help improve enrollment.
Section 3.3.1 Inclusion Criteria	Allowed enrollment of subjects who are treated with a first- or second-generation TKI in combination with a VEGF inhibitor	EGFR TKI plus VEGF inhibitor has been approved as 1L therapy for EGFR-mutated NSCLS in Europe and Japan.
Synopsis Section 1.1.5 Stratification by PD-L1 Expression, smoking history, brain metastasis and Osimertinib Section.4 Method of Assigning Subject Identification	Stratification criteria were changed to add prior osimertinib use	Prior osimertinib treatment was added as a stratification factor to better understand the impact of pretreatment with osimertinib on the clinical benefit of nivolumab plus platinum chemotherapy in the NSCLC subjects with EGFR mutation.
Section 1.3.3 Table 5.1-3 Follow-up Procedural Outline Section 8.4.7 Other Analyses	Added efficacy evaluation of nivolumab plus chemotherapy vs. chemotherapy in participants after next line of treatment (ie, PFS2) as exploratory objective	Additional data collection and analyses of subsequent cancer therapy and subsequent outcomes will be useful in characterizing clinical benefit of study treatments.
Synopsis	Allowed T790M mutation	Improve the enrollment by

Summary of key changes of Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.1 Study Design and Duration Section 3.3.1 Inclusion Criteria Table 5.1-1 Screening Procedures Section 5.6.1 Tumor Tissue Specimens	confirmation testing using tumor tissues and screening testing using blood sample to be performed at local laboratory for subjects who failed 1L first- or second-generation EFGR TKI.	allowing validated testing to be performed at local laboratory.
Section 3.3.1 Inclusion Criteria Number 2, Letter F Section 3.1 Study Design and Duration Table 5.1-2 On-treatment Procedural Outline	Allowed the approval of Medical Monitor for archival tissues obtained more than 6 months prior to the study treatment.	Improve the enrollment by allowing the archival tissues more than 6 months prior to the study treatment at discretion of investigator and Medical Monitor
Synopsis Section 8.1 Sample Size Determination	Sample size and power analyses were updated with additional subjects in Arms A and C	Updated sample size allows sufficient power to evaluate OS benefit in nivolumab plus chemotherapy vs. chemotherapy in additional to the primary PFS benefit
Section 3.3.2 Exclusion Criteria Section 3.4.1 Prohibited and/or Restricted Treatments	Excluded live/attenuated vaccine within 30 days of first treatment	Align with nivolumab program standards for safety
Section 4.5.1.2 Nivolumab plus Pemetrexed/Carboplatin	The carboplatin dose may remain the same if the subject's weight is within 10% of the baseline weight or prior dose weight.	Added to provide clarity in dosing instructions for safety
Section 8.5 Interim Analyses	Interim analyses for OS was added	As part of updated study design and statistical analyses, an Interim analyses was added
Title Page	Updated study personnel	Updated study personnel
Synopsis	Minor formatting and typographical corrections	Minor, therefore have not been summarized

Summary of key changes of Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Multiple sections	Editorial changes for clarity	Improve the clarity of the operational requirements
Appendix 2 Management Algorithms for Immuno-Oncology Agents Appendix 4 Women of Childbearing Potential Definitions and Methods of Contraception	Updated Appendix 2 Management Algorithms for Immuno-Oncology Agents and Appendix 4 Women of Childbearing Potential Definitions and Methods of Contraception	Appendices were updated to align with program standards for safety

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