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Date: 09-Dec-2015
Revised Date 11-Jan-2018

Clinical Protocol CA209568

A Study of Nivolumab in Combination with Ipilimumab (part 1); and Nivolumab plus Ipilimumab in Combination with Chemotherapy (part 2) as First Line Therapy in Stage IV Non-Small Cell Lung Cancer (NSCLC)

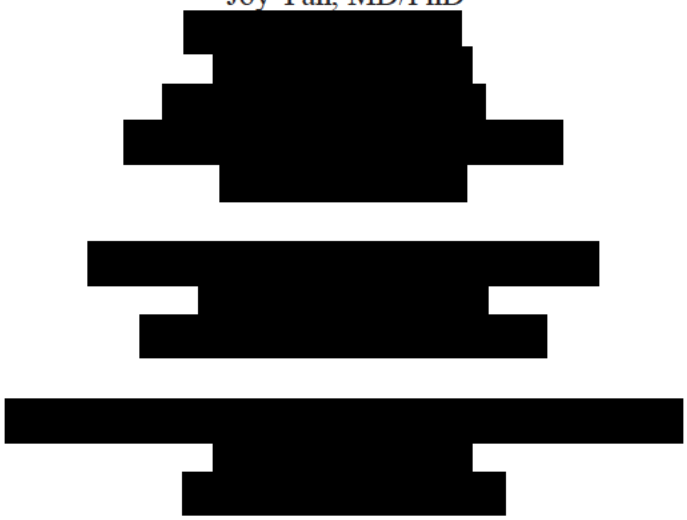
CheckMate 568, CHECKpoint pathway and nivolu**MA**b clinical **T**rial **E**valuation 568)

Revised Protocol Number: 06

Includes Administrative Letter 02

Study Director/Medical Monitor

Joy Yan, MD/PhD



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

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 06	11-Jan-2018	• Removed retreatment with nivolumab and ipilimumab for subsequent disease progression for up to 1 additional year [redacted] • Updated protocol with current contraceptive language • Updated protocol with current program treatment guidelines
Administrative Letter 02	09-Oct-2017	• Remove EUDRACT number
Revised Protocol 05	28-Jul-2017	• Part 2 randomization phase was deleted from the study. Subsequently, the Part 2 randomization objectives, endpoints, analyses, and descriptions were removed. • Part 2 Safety Lead-in was modified and includes new [redacted] analyses, safety definitions, and additional language. • Additional research collection with residual sample storage was added.
Revised Protocol 04	13-Apr-2017	Incorporates Amendment 04
Amendment 04	13-Apr-2017	• Amendment 04 changes the primary objective to progression-free survival and secondary objective to overall survival with subsequent changes to endpoints, analyses, and sample size. • [redacted] • Chemotherapy dosing and modifications were updated. • Interim analyses were removed.
Revised Protocol 03	18-Jan-2017	Incorporates Amendment 03
Amendment 03	18-Jan-2017	[redacted] Updated tables 5.1-2 and 5.6.2.6-1 [redacted] Inserted the dose modification instruction of Cisplatin in tables 4.5.3.2-1 and 4.5.3.4-1.The table was inadvertently modified in previously published version of the protocol. Corrected typographical errors throughout the protocol
Revised Protocol 02	07-Dec-2016	Incorporates Amendment 02
Amendment 02	07-Dec-2016	The study is expended by adding a randomized phase III part after completing enrollment to initial study. The treatment design is adding 2 cycles of chemotherapy as induction with nivolumab +ipilimumab, followed by nivolumab + ipilimumab until progression. A safety lead in of 28 patients will be conducted first to evaluate safe dose levels. After these subjects have been treated and followed for at least 9 weeks on study a decision will be made on the dose level for the randomization phase of part 2. 420 subjects will be randomized to treatment arm and control arm. The primary endpoint for part 2 is overall survival with nivolumab and ipilimumab plus chemotherapy vs. chemotherapy alone.

Document	Date of Issue	Summary of Change
Administrative Letter 01	14-Oct-2016	Section 4.5.4.1 Criteria to Resume Nivolumab Dosing. Corrected a typographical error found in Revised Protocol v01 dated 21Sep2016, to the sixth bullet in regards to prednisone dosing. The ≥ sign was inadvertently used in lieu of the ≤ sign in front of the equivalent dose of prednisone 10mg/day.
Revised Protocol 01	21-Sep-2016	Incorporates Amendment 01
Amendment 01	21-Sep-2016	To increase sample size and some language adjustments on study objectives and stat analyses with added population of PD-L1>=50% and efficacy analyses in PD-L1 negative population.
Original Protocol	09-Dec-2015	Not applicable

[redacted]

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 06		
Section Number & Title	**Description of Change**	[redacted]
Synopsis, Schema, Study Design, Figure 3.1.1.1-1 and Figure 3.1.1.2-1, Section 3.1.1.1 and Section 3.1.1.2. Section 3.1.2.1, Table 4.5-1, Table 4.5-2,	Removed retreatment with nivolumab and ipilimumab for subsequent disease progression for up to 1 additional year and added a maximum treatment duration of 2 years,	
Synopsis Secondary Endpoints, Section 1.3.2 Secondary Objectives Part 2, [redacted] Section 5.4.1 Primary Efficacy Assessment Section 8.3.2 Secondary Endpoints	[redacted]	
[redacted]	[redacted]	
Section 3.3.1 Inclusion Criteria, Age and Reproductive Status	Updated section with Highly Effective Contraceptive Methods That Are User Dependent, Highly Effective Methods That Are User Independent, Unacceptable Methods of Contraception, Contraception Guidance for Male Participants with Partner(S) of Child Bearing Potential	

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 06	
Section Number & Title	**Description of Change**
Section 3.3.2 Exclusion Criteria Other Exclusion Criteria 5 e) Section 3.4.1 Prohibited and/or Restricted Treatments	Excluded/prohibited treatment with botanical preparations during study treatment
Section 4.5.1.1 Nivolumab and ipilimumab dosing	Sequence of study treatment administration updated. Additional language added to separate dosing for Part 1 and Part 2
Section 4.5.4.2 Criteria to Resume Ipilimumab Dosing Section 4.5.5.1 Nivolumab Dose Discontinuation	Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
Section 4.5.5.1 Nivolumab Dose Discontinuation	Exceptions for Grade 3 non-skin, drug-related adverse event lasting > 7 days updated
Section 5.3 Safety Assessments	Pulmonary toxicity evaluation added when pulmonary-related signs are present
Section 5.4 Efficacy Assessments	Added the collection of additional imaging that may demonstrate tumor response or progression
Section 5.6 Subheadings Table 5.6.2.6-1	Language added to subheadings to differentiate procedures for Part 1 and Part 2 Table reformatted to identify biomarker collection Part 1 and Part 2
Section 7.1 Data Monitoring Committee	Removed DMC section

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 06		
Section Number & Title	**Description of Change**	[redacted]
[redacted]	Additional research testing results performed locally will be collected.	
All	Update of references Minor formatting and typographical corrections	

SYNOPSIS

Clinical Protocol CA209568

Protocol Title: A Study of Nivolumab in Combination with Ipilimumab (Part 1); and Nivolumab plus Ipilimumab in Combination with Chemotherapy (Part 2) as First Line Therapy in Stage IV Non-Small Cell Lung Cancer (NSCLC)

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

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

Part 2: Nivolumab administered IV and ipilimumab administered IV together with 2 cycles of histology based platinum doublet chemotherapy as induction treatment, followed by nivolumab and ipilimumab until disease progression or unacceptable toxicity. Treatment with nivolumab and ipilimumab will be given for a maximum of 2 years from the start of study treatment in the absence of disease progression or unacceptable toxicity.

The 2 cycles of histology-based platinum doublet chemotherapy include:

Histology-based platinum doublet chemotherapy:

- Squamous histology: Carboplatin AUC6 + Paclitaxel 200 mg/m2
- Non squamous histology: Carboplatin AUC 5 or 6 + pemetrexed 500 mg/m2 or Cisplatin 75 mg/m2 + pemetrexed 500 mg/m2.

Study Phase: 2

Research Hypotheses:

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

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

Objectives:

Part 1

Primary Objectives (Part 1)

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

Secondary Objectives (Part 1)

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

- To evaluate tumor mutation burden as a potential predictive biomarker of efficacy (such as ORR, PFS and OS) of nivolumab in combination with ipilimumab using DNA derived from tumor specimens

[redacted]

Part 2

Primary Objective (Part 2)

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

Secondary Objectives (Part 2)

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

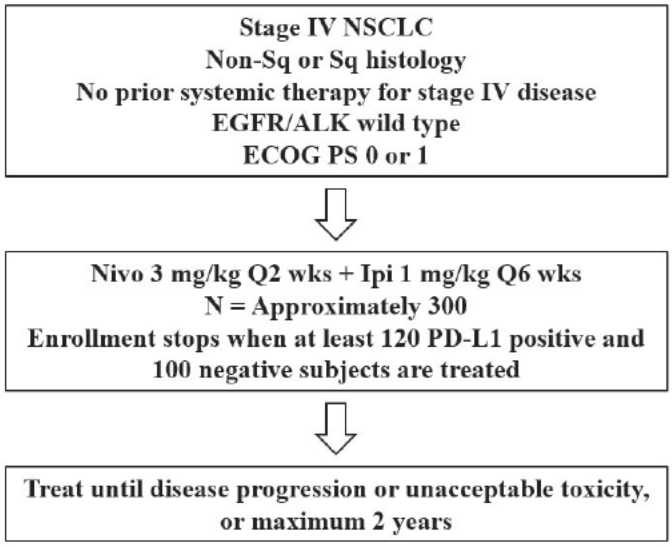
[redacted]

Study Design:

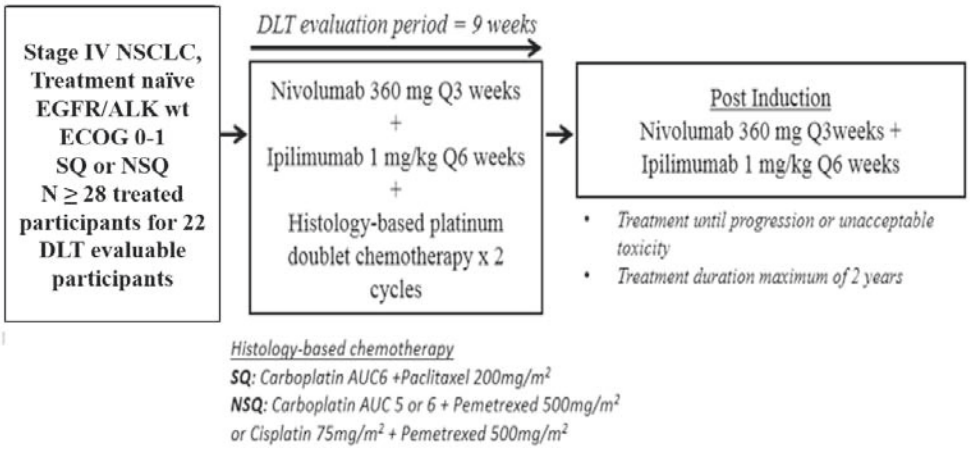
Part 1 Doses of Immunotherapy

- Nivolumab: 3 mg/kg IV q2 weeks
- Ipilimumab: 1 mg/kg IV q6 weeks

Part 1 Schema:



Part 2 Schema for Safety Lead-in:



The safety lead-in phase will be conducted to evaluate safe dose level: approximately 28 subjects (in order to achieve at least 22 DLT evaluable subjects) will receive 2 cycles of induction chemotherapy and nivolumab plus ipilimumab. The starting dose of nivolumab is 360mg every 3 weeks and ipilimumab is 1 mg/kg every 6 weeks.

'Safe' is defined as 25% evaluated subjects or less exhibit DLTs (ie, 5 or less subjects with such events out of 22 DLT evaluable subjects).

A safety assessment will be performed on the first 10 subjects after a minimum of 9 weeks of follow-up. If 20% or less of the first 10 subjects exhibit DLTs (ie, 2 or less subjects with such events), the regimen is determined safe and enrollment in subsequent studies using this combination may start while the safety lead in phase of CA209568 is ongoing. If more than 20% of the first 10 subjects exhibit DLTs, the full safety cohort will be evaluated prior to using this dose regimen in subsequent studies. If more than 25% of the overall DLT evaluable subjects exhibit DLTs, the protocol may be amended to evaluate different dose levels, depending on the toxicities observed.

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

Study Population: Subjects must meet all eligibility criteria specified in Section 3.3 of the protocol, including the following:

Key inclusion criteria include:

- Male and female subjects (≥ 18 years of age).
- Subjects with histologically confirmed stage IV NSCLC (per the 7th International Association for the Study of Lung Cancer classification) squamous or non-squamous histology.
- No prior systemic therapy for stage IV disease. Prior definitive chemoradiation for locally advanced disease is permitted as long as the last administration of chemotherapy or radiotherapy (which ever was given last) occurred at least 6 months prior to enrollment. Locally advanced disease with recurrence after concurrent chemoradiation therapy (stage IIIB, specifically refers to patients with no curative treatment options) is eligible to enroll. Prior adjuvant or neoadjuvant chemotherapy for early stage lung cancer is permitted if completed at least 6 months before initiating study treatment.
- EGFR/ALK wild type, and ECOG PS 0 or 1
- Subjects are to have tumor tissue sample available at central lab for PD -L1 IHC testing during the screening period.
- Measurable disease by CT or MRI per RECIST 1.1 criteria

Subjects in safety lead in phase may initiate therapy before the result of IHC testing once the central lab has confirmed receiving of samples.

Either a formalin-fixed, paraffin-embedded (FFPE) tissue block or unstained tumor tissue sections, with an associated pathology report, must be submitted for biomarker evaluation prior to treatment. The tumor tissue sample may be fresh or archival if obtained within 6 months prior to Part 1 enrollment (archival tissue is to be obtained within 3 months prior to Part 2 enrollment), and there can have been no systemic therapy (eg. adjuvant or neoadjuvant chemotherapy) given after the sample was obtained.

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

Key Exclusion Criteria

- Subjects with known EGFR mutations which are sensitive to available targeted inhibitor therapy (including, but not limited to, deletions in exon 19 and exon 21 [L858R] substitution mutations) are excluded. All subjects with non-squamous histology must have been tested for EGFR mutation status. EGFR test is to be done locally. Use of an FDA-approved or local Health Authority approved test is strongly encouraged. Tests other than PCR or next generation sequencing will be requested to repeat using PCR or next generation sequencing based method. Subjects with non-squamous histology with unknown or indeterminate EGFR status are excluded.
- Subjects with known ALK translocations which are sensitive to available targeted inhibitor therapy are excluded. ALK tests are to be done at local lab and use of a FDA-approved test is strongly encouraged. Subjects with unknown or indeterminate ALK status may be enrolled.
- Subjects with untreated CNS metastases are excluded.

Subjects are eligible if CNS metastases are adequately treated and subjects are neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to first dose. 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 first dose.

- Subjects with carcinomatous meningitis
- 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.
- Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of first treatment. Inhaled or topical steroids, and adrenal replacement steroid > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
- Subjects with history of screen failure to any anti-PD-L1 or anti-PD-L1 antibody clinical trial due to PD-L1-negative status.

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

Study Drugs for CA209568		
Medication	**Potency**	**IP/Non-IP**
Nivolumab	10 mg/ml	IP
Ipilimumab	5 mg/ml	IP
Carboplatin	10 mg/ml	IP
Paclitaxel	6 mg/ml	IP
Pemetrexed	500 mg/vial	IP

Study Drugs for CA209568		
Medication	**Potency**	**IP/Non-IP**
Cisplatin	100 mg/vial (1 mg/mL)	IP

Study Assessments: Subjects will be assessed for PD-L1 expression in tumor cells, and categorized into 4 groups (PD-L1 positive, PD-L1 negative, PD-L1 ≥ 50%, PD-L1 not quantifiable).

PD-L1 status will be determined by Dako PD-L1 IHC 28-8 pharmDx test for immunohistochemical (IHC) staining of PD-L1 protein in the submitted tumor samples

- PD-L1 positive (≥ 1% tumor cell membrane staining in a minimum of a hundred evaluable tumor cells)
- PD-L1 negative (< 1% tumor cell membrane staining in a minimum of a hundred evaluable tumor cells)
- PD-L1 ≥ 50% (≥ 50% tumor cell membrane staining in a minimum of a hundred evaluable tumor cells) and is a subset of all PD-L1 positive subjects.
- PD-L1 not quantifiable is defined as subjects with no quantifiable PD-L1 expression at baseline which is likely due to insufficient tumor biopsy specimens for IHC staining and analysis. For subjects with PD-L1 not quantifiable status tumors key efficacy and safety parameters will be summarized in a descriptive way.

On-study tumor assessments by CT or MRI will begin 6 weeks post first dose date (+/- 7 days) and be performed every 6 weeks (+/- 7 days) until week 48. After week 48, tumor assessments will be performed every 12 weeks (+/- 7 days) until disease progression is documented or treatment is discontinued (whichever occurs later).

Treatment beyond initial RECIST 1.1 defined progression is permitted in subjects receiving nivolumab and ipilimumab containing treatment if the subject has investigator assessed clinical benefit and is tolerating nivolumab plus ipilimumab. Subjects receiving investigational treatment beyond investigator-assessed progression must also continue tumor assessments until such treatment has been discontinued (See Section 4.5.6).

OS will be followed continuously while subjects are on the study drugs and every 3 months via in-person or phone contact after subject discontinued the study drugs.

[redacted]

Primary Endpoints:

Part 1:

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

Objective response rate (ORR) is based on blinded independent central review assessment per RECIST 1.1 criteria. ORR is defined as the number of subjects with a best overall response (BOR) of confirmed CR or PR, divided by the number of treated subjects among PD-L1 positive or PD-L1 negative subjects or all treated subjects. BOR is defined as the best response designation recorded between baseline and the date of objectively documented progression per RECIST 1.1 or the date of initiation of palliative local therapy or the date of initiation of subsequent anticancer therapy, whichever occurs first.

Blinded independent central review determined PFS is defined as the time from the first dosing date for treated subjects in Part 1) to the date of the first documented tumor progression as determined by blinded independent central review (per RECIST 1.1), or death due to any cause. 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 will be censored at the first dose date for subjects. Subjects who started any palliative local therapy or subsequent 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 the palliative local therapy or subsequent anti-cancer therapy, whichever procedure occurred first.

Part 2:

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

Secondary Endpoints:

Part 1:

- ORR by blinded independent central review per RECIST 1.1 in all treated subjects treated with nivolumab in combination with ipilimumab as first line therapy
- Progression free survival (PFS) based on blinded independent central review assessment per RECIST 1.1
- Overall survival (OS)
- ORR, PFS and OS by PD-L1 expression levels
- Tumor cell total somatic mutations and their association with ORR, PFS, and OS

Part 2:

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

OS is defined as the time between the date of the first dosing date and the date of death due to any cause.

Analyses: Demographics and baseline laboratory results will be summarized using descriptive statistics for all treated subjects in Part 1 and all treated subjects in Part 2.

Among all treated subjects, the ORR and PFS will be determined by investigator assessment and will be summarized by binomial response rates and their corresponding two-sided 95% exact CIs using Clopper-Pearson method. In parts 1 and 2, separately, time to event distribution such as PFS and OS will be estimated using Kaplan Meier techniques. To further characterize the response, time to objective response, depth of response, and BOR by response category will be summarized using descriptive statistics.

The safety analysis will be performed in all treated subjects. Descriptive statistics of safety will be presented using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

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[redacted]

1.2 Research Hypothesis

Part 1: In subjects with PD-L1positive (membranous staining in ≥ 1% tumor cells) and negative (membranous staining in < 1% tumor cells) stage IV NSCLC, the administration of nivolumab in combination with ipilimumab as first line treatment will lead to clinical benefit as demonstrated by a clinically meaningful objective response rate (ORR) and duration of response.

In individual patient data meta-analysis of 2968 patients suggests that cisplatin or carboplatin based chemotherapy has response rate of 30% (cisplatin based chemo) or 24% (carboplatin based chemo).[25] Clinically meaningful objective response rate is defined as higher than 30% which is the ORR of cisplatin based standard of care chemotherapy, and/or considerably longer duration of response.

Part 2: nivolumab and ipilimumab combined with standard of care chemotherapy are tolerable in first line stage IV NSCLC unselected for PD-L1 expression.

1.3 Objectives(s)

1.3.1 Primary Objectives

Part 1:

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

Part 2:

Primary Endpoints:

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

1.3.2 Secondary Objectives

Part 1:

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

Part 2:

Secondary Endpoints:

- To evaluate ORR, PFS by investigator assessment per RECIST 1.1, and OS

[redacted]

[redacted]

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol 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 BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

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

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

2.2 Institutional Review Board/Independent Ethics Committee

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

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

2.3 Informed Consent

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

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

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

Investigators must:

A. 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.
B. Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
C. 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.

D. 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.

E. 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.

F. 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

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

- PD-L1 positive (≥ 1% tumor cell membrane staining in a minimum of a hundred evaluable tumor cells)
- PD-L1 ≥ 50% (≥ 50% tumor cell membrane staining in a minimum of a hundred evaluable tumor cells) and is a subset of all PD-L1 positive subjects.

- PD-L1 negative (< 1% tumor cell membrane staining in a minimum of a hundred evaluable tumor cells)
- PD-L1 not quantifiable (subjects with tumor biopsy specimens without quantifiable PD-L1 expression)

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

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

For the Part 2 safety lead in, only receipt of suitable tissue by the central lab is required for treatment.

3.1.1 Study design

3.1.1.1 Part 1 study design

Nivolumab is administered IV over 30 minutes at 3 mg/kg every 2 weeks combined with ipilimumab administered IV over 30 minutes at 1 mg/kg every 6 weeks until progression, unacceptable toxicity, or other reasons specified in the protocol. In study CA209568, treatment with nivolumab with ipilimumab will be given for a maximum of 2 years from the start of study treatment in the absence of disease progression or unacceptable toxicity.

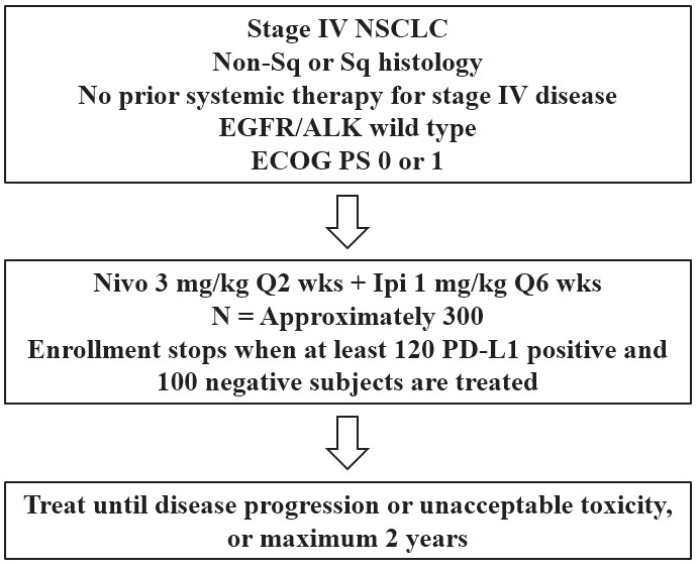
Treatment beyond initial investigator-assessed RECIST 1.1 defined progression is permitted if the subject as specified in Section 4.5.6 has investigator assessed clinical benefit and is tolerating nivolumab and ipilimumab.

On-study tumor assessments will begin 6 weeks post first dose date (+/-7 days) and be performed every 6 weeks (+/- 7 days) until week 48. After week 48, tumor assessments will be performed every 12 weeks (+/- 7 days) until blinded independent central review assessed progression. Subjects received nivolumab plus ipilimumab beyond investigator-assessed progression must also continue tumor assessments until further progression at subsequent tumor assessment as indicated in Section 4.5.6.

The study design schematic is presented in Figure 3.1.1.1-1.

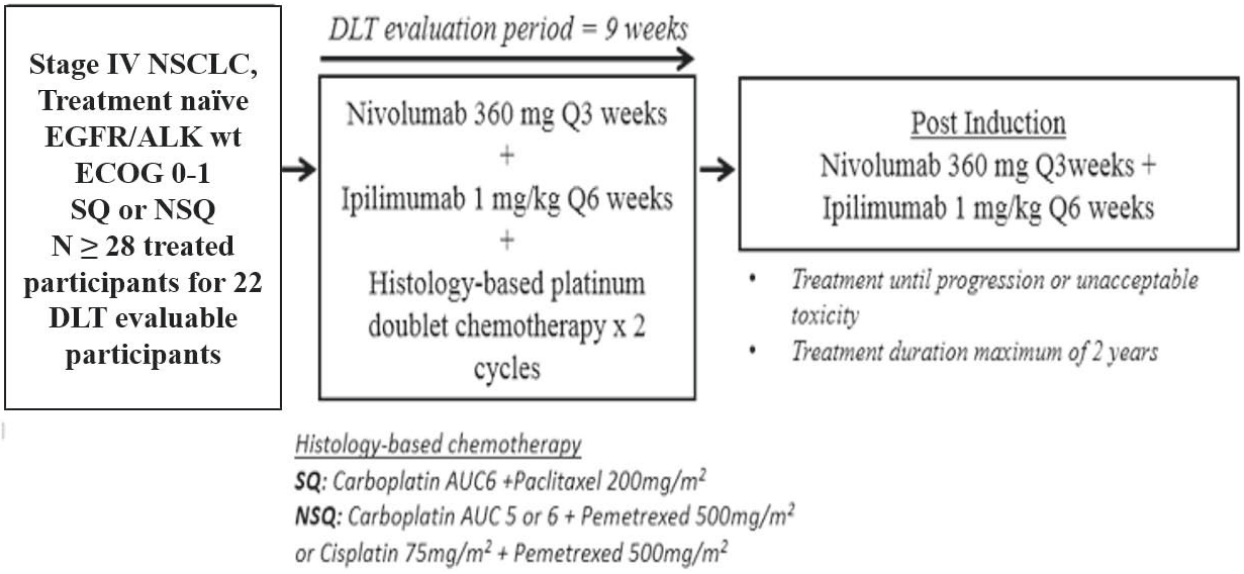
Figure 3.1.1.1-1: Part 1 Study Design Schematic

Part 1:



3.1.1.2 Part 2 study design

Figure 3.1.1.2-1: Part 2 Study Design Schematic



Safety lead-in phase will be conducted to evaluate safe dose level for the Part 2 study. Approximately 28 subjects will receive 2 cycles of induction chemotherapy and nivolumab plus ipilimumab. The starting dose of nivolumab is 360mg every 3 weeks and ipilimumab is 1 mg/kg every 6 weeks. Nivolumab will be administered with ipilimumab, plus 2 cycles of histology based platinum doublet chemotherapy as follows:

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

- Non-squamous histology: Carboplatin AUC 5 or6 + pemetrexed 500mg/m^2 or Cisplatin 75mg/m^2 + pemetrexed 500mg/m^2.

After above 2 cycles of induction therapy, nivolumab is administered IV over 30 minutes combined with ipilimumab administered IV over 30 minutes until progression, unacceptable toxicity, or other reasons specified in the protocol. In study CA209568, treatment with nivolumab and ipilimumab will be given for a maximum of 2 years from the start of study treatment in the absence of disease progression or unacceptable toxicity.

Treatment beyond initial investigator assessed RECIST 1.1 defined progression is permitted if the subject as specified in Section 4.5.6 has investigator assessed clinical benefit and is tolerating nivolumab and ipilimumab.

On-study tumor assessments will begin at week 6 post first dose date (+/- 7 days) and be performed every 6 weeks (+/- 7 days) until week 48. After week 48, tumor assessments will be performed every 12 weeks (+/- 7 days) until investigator assessed progression or treatment discontinuation (whichever occurs later). Subjects receiving nivolumab plus ipilimumab beyond investigator assessed progression must also continue tumor assessments until further progression at subsequent tumor assessment as indicated in Section 4.5.6.

3.1.2 Study Phase

3.1.2.1 Screening Phase

- Begins by establishing the subject's initial eligibility and signing of the informed consent (ICF).
- Subject is enrolled using the Interactive Web Response System (IWRS).
- Tumor tissue (archival or recent tumor biopsy) must be submitted by the site to a third party vendor for determination of PD-L1 status. An email/fax communication will be sent by the third party vendor to site for confirmation upon receiving tumor tissue.
- Subject is assessed for study eligibility as described in Table 5.1-1.
- All screening assessments and procedures must be performed within 28 days prior to treatment.

Part 1:

Subjects can initiate therapy before the result of IHC testing.

Part 1 treatment

- Nivolumab 3 mg/kg IV will be administered every 2 weeks.
- Ipilimumab 1 mg/kg IV will be administered every 6 weeks following the administration of nivolumab.
- On the day of infusion, nivolumab is to be administered first. The second infusion will always be ipilimumab (if ipilimumab is scheduled to be given), and will start at least 30 minutes after completion of the nivolumab infusion.
- Nivolumab 3 mg/kg Q2 weeks and ipilimumab 1 mg/kg Q6 weeks will be continued until the progression of disease, discontinuation due to toxicity, withdrawal of consent, or study closure. In study CA209568, treatment with nivolumab with ipilimumab will be given for a maximum

of 2 years from the start of study treatment in the absence of disease progression or unacceptable toxicity.

Part 2

Safety lead-in phase will be conducted to evaluate safe dose level for the subsequent studies using same drug combination. Approximately 28 subjects will receive 2 cycles of induction chemotherapy and nivolumab plus ipilimumab. The starting dose of nivolumab is 360 mg every 3 weeks and ipilimumab is 1 mg/kg every 6 weeks. Subjects can initiate therapy before PD-L1 testing results.

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

- Any Grade 2 drug-related uveitis or eye pain that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 2 drug-related pneumonitis or interstitial lung disease that does not resolve to dose delay and systemic steroids in 14 days (radiologic changes may take longer to resolve). The management algorithm for pneumonitis or pulmonary toxicity can be found in the appendix and in the current Investigator Brochure.[22]
- Any Grade 3 non-skin drug-related adverse event with the exception of laboratory abnormalities that cannot be alleviated (defined as returning to grade 1, radiologic changes may take longer to resolve) or controlled by appropriate care within 14 days (appropriate care being defined as treatment outlined in AE management algorithms in the investigators brochure).
- Any Grade 4 drug-related adverse event including laboratory abnormalities except Grade 4 leukopenia or neutropenia lasting < 14 days and asymptomatic amylase/lipase elevation
- Any of the following drug-related hepatic function laboratory abnormalities:
  - AST or ALT >5-10x ULN for > 2 weeks
  - AST or ALT > 10x ULN
  - Total bilirubin > 5 x ULN
  - Concurrent AST or ALT > 3x ULN and total bilirubin > 2x ULN
  - Grade 3 thrombocytopenia associated with bleeding

*During the first 9 weeks: subjects should discontinue treatment if they experience any adverse event, laboratory abnormality or intercurrent illness (regardless of causality) which, in the opinion of the investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing. Such discontinuation, however, will not be considered a DLT unless it meets at least one of the DLT criteria defined above. Treatment delay, modification and discontinuation criteria are to be followed for management of safety lead in subjects as outlined in Sections 4.5.2, 4.5.3, and 4.5.5.

Subjects in safety lead in will follow Part 2 study procedures, and will have on study tumor assessment as outlined in Table 5.1-3. Investigator assessed efficacy evaluation will be based on RECIST 1.1. Independent radiology central review is not required for safety lead in subjects. Upon completion of dosing, subjects will enter Follow-up phase Table 5.1-4.

Nivolumab and ipilimumab will be continued until the progression of disease, discontinuation due to toxicity, withdrawal of consent, for a maximum of 2 years from the start of study treatment in the absence of disease progression, or unacceptable toxicity.

3.1.3 Post-Treatment Follow-up

The post-treatment follow-up begins when the decision to discontinue a subject from all treatment is made.

- 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 5.1-4 until progression confirmed by blinded independent central review.
- At the time of investigator-assessed radiographic progression per RECIST 1.1, sites must request a blinded independent central review from the third party radiology vendor for subjects in Part 1, as specified in Section 7.2.
- 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 Section 6.
- After completion of the first two 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 5.1). BMS may request that survival data be collected on all treated subjects outside of the protocol defined window. At that time of this request, each subject will be contacted to determine their survival status unless the subject had withdrawn consent for all contact.

3.1.4 Duration of Study

Part 1:

The analysis of the primary endpoint ORR will be performed at least six month after last subject first treatment. Additional survival follow-up may continue for up to 5 years from the primary analysis. The study will end once survival follow-up has concluded.

Part 2:

The duration of the study is from the start of safety-lead in phase until the analyses of PFS and OS are complete, about 13.5 months after first subject in Part 2 is treated. Additional survival follow-up may continue for up to 5 years from the primary analysis.

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. Study drug will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of BMS. BMS reserves the right to terminate access to BMS supplied study drug if any of the following occur: a) the marketing application is rejected by 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) ECOG Performance Status of 0-1

b) Subjects with histologically confirmed stage IV NSCLC per the 7th International Association for the Study of Lung Cancer classification (IASLC)[53] of squamous or nonsquamous histology, with no prior systemic anticancer therapy (including EGFR and ALK inhibitors) given as primary therapy for advanced or metastatic disease. Prior definitive chemoradiation for locally advanced disease is permitted as long as the last administration of chemotherapy or radiotherapy (which ever was given last) occurred at least 6 months prior to enrollment. Locally advanced disease with recurrence after chemoradiation therapy (stage IIIB disease, specifically refers to patients with no curative options), is eligible to enroll. Prior adjuvant or neoadjuvant chemotherapy for early stage lung cancer is permitted if completed at least 6 months prior to initiating study treatment.

c) Measurable disease by CT or MRI per RECIST 1.1 criteria (Appendix 3); radiographic tumor assessment performed within 28 days before treatment.

   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.

d) Subjects are to have tumor tissue sample available at central lab for PD -L1 IHC testing during the screening period. Subjects can initiate therapy before the result of IHC testing for Part 1 subjects.

Part 2 subjects must have PD-L1 IHC testing performed by the central lab. If results are not available during screening period, participants can initiate treatment. Subjects in safety lead in phase may initiate therapy before the result of PD-L1 IHC testing.

Subjects in safety lead in phase may initiate therapy before the result of PD-L1 IHC testing.

Either a formalin-fixed, paraffin-embedded (FFPE) tissue block or unstained tumor tissue sections, with an associated pathology report, must be submitted for biomarker evaluation prior to treatment. The tumor tissue sample may be fresh or archival if obtained within 6 months prior to Part 1 enrollment,(archival tissue is to be obtained within 3 months prior to Part 2 enrollment), and there can have been no systemic therapy (eg, adjuvant or neoadjuvant chemotherapy) given after the sample was obtained.

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

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

f) Screening laboratory values must meet the following criteria (using CTCAE v4):
   i) WBC ≥ 2000/μL
   ii) Neutrophils ≥ 1500/μL
   iii) Platelets ≥ 100 x 10^3/μL
   iv) Hemoglobin ≥ 9.0 g/dL
   v) Serum creatinine ≤ 1.5 x ULN or calculated creatinine clearance ≥ 50 mL/min (using the Cockcroft Gault formula)

$$\text{Female CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$$

$$\text{Male CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$$

   vi) AST/ALT ≤ 3.0 x ULN (≤ 5 x ULN if liver metastases are present)
   vii) Total bilirubin ≤1.5 x ULN except subjects with Gilbert Syndrome who must have a total bilirubin level < 3.0 mg/dL).

Subject Re-enrollment: This study permits the re-enrollment of a subject who has discontinued the study as a pre-treatment failure (ie, subject has not been treated). If re-enrolled, the subject must be re-consented.

3. Age and Reproductive Status

a) Males and Females, ages ≥ 18 years of age
b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.
c) Women must not be breastfeeding
d) WOCBP must agree to follow instructions for methods(s) of contraception for the duration of treatment with nivolumab and 5 months after the last dose of nivolumab {ie 30 days (duration of ovulatory cycle) plus the time required for nivolumab to undergo approximately five half-lives }
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 Part 2 subjects).
f) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with nivolumab and up to

7 months after the last dose of nivolumab {ie 90 days (duration of sperm turnover) plus the time required for nivolumab to undergo approximately five half-lives}.

g) Males who are sexually active with WOCBP must agree to follow instructions for methods(s) 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 poste treatment completion or a duration specified by the local labels of the chemotherapy drugs received, whichever is longer (for Part 2 subjects).
h) Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However they must still undergo pregnancy testing as described in these sections.

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy.

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

Local Laws and Regulations may require use of alternative and/or additional contraception methods.

At a minimum, subjects must agree to use one highly effective method of contraception as listed below:

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[b] – oral – intravaginal – 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 [b] • Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and intrauterine hormone-releasing system (IUS)[c] • Intrauterine device (IUD)[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 drug. 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 drug, 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

Unacceptable Methods of Contraception*
• 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 • 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 are required to use a condom for study duration and until end of relevant systemic exposure defined as 7 months after the end of study treatment.
- 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 7 months after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 7 months after the end of study treatment.
- Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of study treatment.

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Subjects with known EGFR mutations which are sensitive to available targeted inhibitor therapy (including, but not limited to, deletions in exon 19 and exon 21 [L858R] substitution mutations) are excluded. All subjects with non-squamous histology must have been tested for EGFR mutation status. EGFR test is to be done locally. EGFR test is not provided by central lab. Use of an FDA-approved or local Health Authority approved test is strongly encouraged. Subjects of non-squamous histology with unknown or indeterminate EGFR status are excluded.

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) Subjects with untreated CNS metastases are excluded. Subjects are eligible if CNS metastases are adequately treated and subjects are neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to first treatment. 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 first treatment.

d) Subjects with carcinomatous meningitis

2. Medical History and Concurrent Diseases

a) Subjects must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before first treatment.

b) Subjects with previous malignancies (except non-melanoma skin cancers, and in situ cancers such as the following: bladder, gastric, colon, cervical/dysplasia, melanoma, or breast) are excluded unless a complete remission was achieved at least 2 years prior to first treatment and no additional therapy is required or anticipated to be required during the study period.

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 of first 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). (Testing for HIV must be performed at sites mandated by local requirements.)

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

3. Physical and Laboratory Test Findings

a) Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic infection

b) Subjects with ≥Grade 2 peripheral neuropathy

4. Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to study drug components

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

c) Any other serious or uncontrolled medical disorder, active infection, physical exam finding, laboratory finding, altered mental status, or psychiatric condition that, in the opinion of the investigator, would limit a subject's ability to comply with the study requirements, substantially increase risk to the subject, or impact the interpretability of study results
d) Subjects with a history of screen failure to any anti-PD-1 or anti-PD-L1 antibody clinical trial due to PD-L1 negative status.
e) Treatment with botanical preparations (eg herbal supplements or traditional Chinese medicines) intended for general health support or to treat the disease under study within 2 weeks prior to randomization/treatment. Refer to Section 3.4.1 for prohibited therapies.

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.

[redacted]

[redacted]

[redacted]

[redacted]

3.5 Discontinuation of Subjects following any Treatment with Study Drug

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

- Subject's request to stop study treatment
- Any clinical 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 (e.g., infectious disease) illness
- Pregnancy*

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

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

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 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 to occur 115 days from Follow-Up Visit 1 (+/- 7 days). Survival Follow-Up Visits to occur approximately every 3 months from Follow-Up Visit 2. Survival Follow-up visits may be performed by phone contact or office visit.

BMS may request that survival data be collected on all subjects outside of the protocol defined window. 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**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

3.6.2 Lost to Follow-Up

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

If investigator's use of third party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained

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

4 STUDY DRUG

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

Table 4-1: Product Description - Treatment Phase

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/Label Type	Secondary Packaging (Qty)/Label Type	Appearance	Storage Conditions (per label)
BMS-936558-01 nivolumab Solution for Injection[a]	100 mg (10 mg/mL)	10 mL per vial/ Open-label	5 or 10 vials per carton/ Open-label	Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8° C. Protect from light and freezing
Ipilimumab Solution for Injection	200 mg (5mg/mL)	40 mL vial/Open-label	4 vials per carton/Open-label	Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8° C. Protect from light and freezing
Carboplatin Solution for Injection[b]	450 mg/vial (10 mg/mL)	45 mL per vial/ Open label	4 vials per carton/Open-label	Clear, colorless or slightly yellow solution	Store at or below 25° C Protect from light
Paclitaxel Solution for Injection[b]	100 mg/vialb (6 mg/mL)	16.7 mL vial/ Open-label	4 vials per carton/Open-label	Clear, colorless or slightly yellow viscous solution	Store at 15°C-30°C. Protect from light.
Pemetrexed Powder for Concentrate for Solution for Infusion[b]	500 mg/vial	500 mg per vial/ Open label	1 vial per carton/ Open-label	White to either light yellow or green-yellow lyophilised powder	Store at 25° C. Excursions permitted (15-30° C)
Cisplatin Solution for Infusion[b]	100 mg/vial (1 mg/mL)	100 mL per vial/ Open-label	4 vials per carton Open-label	Clear, colorless solution	Do not store above 25° C. Do not refrigerate or freeze. Store in original container.

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

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

4.1 Investigational Product

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

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

In this protocol, investigational product(s) is/are:

- Nivolumab
- Ipilimumab
- Carboplatin
- Pemetrexed
- Paclitaxel
- Cisplatin

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.

In this protocol, non-investigational product(s) is/are: any medications used to treat nivolumab/ipilimumab or chemotherapy infusion-related reactions (eg, steroids). These non-investigational products should be sourced by the investigator sites if available and permitted by local regulations.

4.3 Storage and Dispensing

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 immediately.

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

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

Infusion-related supplies (eg, IV bags, in-line filters, 0.9% NaCl solution) will not be supplied by the sponsor and should be purchased locally if permitted by local regulations.

For nivolumab and ipilimumab, please refer to the current version of the Investigator Brochures and/or pharmacy reference sheets for complete storage, handling, dispensing, and infusion information.

Nivolumab is to be administered as an approximately 30-minute IV infusion. At the end of the infusion, flush the line with a sufficient quantity of normal saline or dextrose solution. Ipilimumab is to be administered as an approximately 30-minute IV infusion. At the end of the infusion, flush the line with a sufficient quantity of normal saline or 5% dextrose solution. When both study drugs are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the infusion. The second infusion will always be ipilimumab, and will start at least 30 minutes after completion of the nivolumab infusion.

4.4 Method of Assigning Subject Identification

After the subject's initial eligibility is established and informed consent has been obtained, the subject must be enrolled into the study by calling an interactive web response system (IWRS) to obtain the subject number. Every subject that signs the informed consent form must be assigned a subject number in IWRS. 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
- Subject number
- Date of birth

Subjects enrolled will be grouped according to PD-L1 status (positive, negative, or not quantifiable, using membranous staining in ≥ 1% tumor cells vs membranous staining in < 1% tumor cells). PD-L1 expression data will be transferred directly from analyzing lab to IWRS. IWRS will be used to track the enrollment number.

Part 1:

Enrollment will end after the last 120 PD-L1 positive and 100 PD-L1 negative subjects are treated, whichever comes later (part 1 enrollment target was reached on Nov. 15, 2016. Future enrollment will be in Part 2 only). The exact procedures for using the IWRS will be detailed in the IWRS manual.

Part 2:

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

4.5 Selection and Timing of Dose for Each Subject

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 4.5.2, 4.5.3, 4.5.4 and 4.5.5.

Table 4.5-1: Part 1 Dosing Schedule*

	Week 1 Day 1 ± 3 Days	Week 2	Week 3 Day 1 ± 3 Days	Week 4	Week 5 Day 1 ± 3 Days	Week 6
Part 1 Nivolumab 3 mg/kg q 2 weeks + Ipilimumab 1 mg/kg q 6 weeks[a]	Day 1 Nivolumab + Ipilimumab		Day 1 Nivolumab		Day 1 Nivolumab	

a continues until disease progression, discontinuation due to unacceptable toxicity, withdrawal of consent, or study closure, for a maximum of 2 years from the start of study treatment in the absence of disease progression or unacceptable toxicity.

* Both nivolumab and ipilimumab should be administered as 30 minute infusions. Nivolumab is to be administered first. The second infusion will be ipilimumab, and will start at least 30 minutes after completion of the nivolumab infusion

Table 4.5-2: Part 2 Dosing Schedule*

	Week 1 Day 1 ± 3 Days	Wk 2	Wk 3	Week 4 Day 1 +/- 3 days	Wk 5	Wk 6	Week 7 Day 1 ± 3 Days
Safety lead in phase							
Part 2 Safety Lead-in Nivolumab + ipilimumab + Platinum-doublet chemotherapy q 3wk x 2 cycles followed by nivolumab (360 mg q 3wks) + ipilimumab 1mg/kg q 6wks[a]	Cycle 1 Nivolumab + Ipilimumab + Histology based chemotherapy			Cycle 2 Nivolumab + Histology based chemotherapy			Cycle 3 Nivolumab + Ipilimumab

* Both nivolumab and ipilimumab should be administered as 30 minute infusions. Nivolumab is to be administered first. The second infusion will be ipilimumab, and will start at least 30 minutes after completion of the nivolumab infusion. Platinum-doublet will start at least 30 minutes after completion of the nivolumab or ipilimumab infusion (if ipilimumab is scheduled to be given).

[a] Continues until disease progression, discontinuation due to unacceptable toxicity, withdrawal of consent, or study closure. A maximum of 2 years from the start of study treatment in the absence of disease progression or unacceptable toxicity.

4.5.1 Dosing

4.5.1.1 Nivolumab and ipilimumab dosing

For Part 1, subjects will receive treatment with nivolumab as a 30 minute infusion 3 mg/kg every 2 weeks and ipilimumab as a 30 minute infusion 1 mg/kg every 6 weeks, starting on Day 1, until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first. Nivolumab and ipilimumab will be continued until the progression of disease, discontinuation due to toxicity, withdrawal of consent, or study closure. In study CA209568, treatment with

nivolumab with ipilimumab will be given for a maximum of 2 years from the start of study treatment in the absence of disease progression or unacceptable toxicity. Participants should begin study treatment within 3 calendar days of treatment assignment.

For Part 1 and Part 2: When study treatments (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 flush of diluent to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be the ipilimumab study treatment and will start after the infusion line has been flushed, filters changed and patient has been observed to ensure no infusion reaction has occurred. Nivolumab and ipilimumab may be diluted in 0.9% Sodium Chloride Solution or 5% Dextrose solution.

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 prior dose, the dose must be recalculated. All doses should be rounded to the nearest milligram. There will be no dose modifications allowed.

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

Subjects should be carefully monitored for infusion reactions. If an acute infusion reaction is noted, subjects should be managed according to Section 4.5.8.

Doses of nivolumab and/or ipilimumab may be interrupted, delayed, or discontinued depending on how well the subject tolerates the treatment. Dosing visits are not skipped, only delayed. For more details, see Sections 4.5.2 (dose delays), 4.5.4 (resuming treatment), and 4.5.5 (discontinuation).

For Part 2 only: On cycle 1 day 1, subjects will receive nivolumab by 30 minute infusion, then followed by ipilimumab by 30 minute infusion, followed by histology-based chemotherapy. One cycle is every 3 weeks. On cycle 2 day 1, subjects will receive 30 minute nivolumab infusion, followed by histology based chemotherapy. In safety lead-in phase, nivolumab dose during induction is 360 mg, and ipilimumab dose is 1 mg/kg. Participants should begin study treatment within 3 calendar days of treatment assignment.

At the time of completion of 2 cycles of therapy, subjects who have not experienced disease progression will continue to receive nivolumab at a dose of 360 mg as 30 minute infusion every 3 weeks, and ipilimumab 1 mg/kg as 30 minute infusion IV every 6 weeks. Treatment will continue until progression, unacceptable toxicity, withdrawal of consent, for a maximum of 2 years from the start of study treatment in the absence of disease progression or unacceptable toxicity. The maximum 2 years of treatment also applies to treatment beyond progression. Dosing calculations should be on the body surface area calculation and maybe 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.

4.5.1.2 Part 2-Chemotherapy Dosing for Safety Lead-in

Histology based chemotherapy:

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

Non squamous histology:

- Carboplatin AUC 5 or 6 + pemetrexed 500 mg/m^2 or
- Cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2

All chemotherapy agents preparation, premedication, administration, monitoring, and management of complications are to follow local prescription guideline and regulation. The dose of chemotherapy may be capped per local standards.

Dosing calculations should be on the body surface area calculation and maybe 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

4.5.1.2.1 Paclitaxel

Subjects may receive paclitaxel 200 mg/m^2 as a 180-minute IV infusion with carboplatin at a dose of AUC 6 as a 30-minute IV infusion, on Day 1 of a 3-week cycle, or at doses per the local prescribing information. The infusion time can follow local institutional standard. Paclitaxel is to be administered before carboplatin.

Paclitaxel 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% of the baseline weight or prior dose weight.

Premedications for use with paclitaxel: Oral corticosteroid should be given according to local standard at a dose equivalent to dexamethasone 20 mg 12 hours and 6 hours prior to paclitaxel administration. Oral or intravenous (IV) diphenhydramine (or its equivalent) 50 mg and H2-blocker (per local standard of care) should be administered 30 to 60 minutes prior to paclitaxel infusion.

Doses of Paclitaxel and/or carboplatin may be interrupted, delayed, reduced, or discontinued depending on how well the subject tolerates the treatment.

4.5.1.2.2 Pemetrexed

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.

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 one 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. (Subjects with non-squamous histology may begin folic acid and vitamin B12 prior to treatment in anticipation of pemetrexed).

Doses of pemetrexed may be interrupted, delayed, reduced, or discontinued depending on how well the subject tolerates the treatment.

4.5.1.2.3 Cisplatin

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.

Cisplatin will be administered to subjects at least 30 minutes 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 (per local standards) 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.

Doses of cisplatin may be interrupted, delayed, reduced, or discontinued depending on how well the subject tolerates the treatment See the following sections for more details: 4.5.2 (dose delays), 4.5.3.1, 4.5.3.2, 4.5.3.3, and 4.5.3.4 (dose reductions); 4.5.4 (retreatment), and 4.5.5 (dose discontinuations).

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.

4.5.1.2.4 Carboplatin

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 Cockcroft-Gault formula (see Inclusion criterion 2f in Section 3.3.1) and should include the most recent serum creatinine and most recent weight. NOTE: If calculation of the CrCl by the Cockcroft-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.

Premedications for use with carboplatin: may be employed at the discretion of the Investigator. Carboplatin is to be administered after paclitaxel.

Doses of carboplatin may be interrupted, delayed, reduced, or discontinued depending on how well the subject tolerates the treatment.

4.5.2 Dose Delay Criteria

4.5.2.1 Dose Delay Criteria for Nivolumab and Ipilimumab

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

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. The BMS Medical Monitor should be consulted for such Grade ≥ 3 amylase or lipase abnormalities.
  - 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.)

Rescheduling:

- 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 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 4.5.5.

4.5.2.2 Dose Delay Criteria for Chemotherapy

In Part 2, chemotherapy drugs should be delayed for any of the following on the Day 1 of each cycle:

- Absolute neutrophil count (ANC) ≥ 1500/μL
- Platelets < 100,000/mm3
- 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, if subjects receiving carboplatin with paclitaxel and must discontinue carboplatin, the paclitaxel may be continued at the investigator's discretion. If any non-hematologic adverse event meeting the dose delay criteria above is felt to be related to only one 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 4.5.3.2 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 4.5.4.3).

Part 2 safety lead in: If any adverse event meeting the dose delay criteria for chemotherapy is felt to be related to only one particular agent in the platinum doublet chemotherapy regimen, then that chemotherapy agent alone may be omitted for that cycle while the other agents (nivolumab and one chemotherapy agent) are given. Dosing of nivolumab and both chemotherapy agents should be delayed if criteria for nivolumab or "both platinum-doublet chemotherapy agents" are met. Therefore nivolumab and chemotherapy can be given as combination.

4.5.3 Dose Reductions

4.5.3.1 Dose Reduction for Nivolumab or Ipilimumab in both Part 1 and Part 2

There will be no dose reductions for nivolumab or ipilimumab.

4.5.3.2 Dose Reduction for Chemotherapy in Part 2

Dose reductions of chemotherapy may be required, and will be performed according to Table 4.5.3.2-1. 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.

Table 4.5.3.2-1: Dose Modifications of Chemotherapeutic Agents

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

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

4.5.3.3 Dose Reductions for Hematologic Toxicity

Dose modifications for hematologic toxicities (according to CTCAE version 4) are summarized in Table 4.5.3.3-1. 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 4.5.3.3-1: Dose Modifications for Hematologic Toxicity (Based on Nadir Counts)

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

4.5.3.4 Chemotherapy - Dose Reductions for Non-Hematologic Toxicities

Dose adjustments for chemotherapy for non-hematologic toxicities during treatment are described in Table 4.5.3.4-1. All dose reductions should be made based on the worst grade toxicity. Subjects experiencing any of the toxicities during the previous cycle should have their chemotherapy delayed until retreatment criteria are met and then reduced for all subsequent cycles by 1 dose level or discontinued as appropriate. Dose levels for the two drugs in the platinum-doublet chemotherapy regimen are not linked and may be reduced independently, as summarized in the Table 4.5.3.4-1 below

Table 4.5.3.4-1: Dose Modifications for Non-hematologic Toxicity

Toxicity	Paclitaxel	Carboplatin	Pemetrexed	Cisplatin
Febrile Neutropenia Grade ≥ 3	Reduce one dose level	Reduce one dose level	Reduce one dose level	Reduce one dose level
Diarrhea Grade ≥ 3	Reduce one dose level	No change	Reduce one dose level	No change
Allergic reaction[a] Grade ≥ 3	Discontinue	Discontinue	Discontinue	Discontinue
Neuropathy Grade 2	Reduce one dose level	No change	No change	Reduce one dose level
Neuropathy Grade ≥ 3	Discontinue	Discontinue	Discontinue	Discontinue
Calculated creatinine clearance **< 50 mL/min**	No change	Discontinue if creatinine clearance < 20 ml/min	No change	Discontinue

Table 4.5.3.4-1: Dose Modifications for Non-hematologic Toxicity

Toxicity	Paclitaxel	Carboplatin	Pemetrexed	Cisplatin
Other Grade ≥ 3 toxicity (except for fatigue and transient arthralgia and myalgia)	Adjust as medically indicated	Adjust as medically indicated	Adjust as medically indicated	Adjust as medically indicated

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

4.5.4 Criteria to Resume Dosing

4.5.4.1 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 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 4.5.5) should have treatment permanently discontinued.
- 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 BMS 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.
- 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 BMS Medical Monitor should be consulted prior to resuming nivolumab in such subjects.
- Dose delay of nivolumab which results in treatment interruption of > 6 weeks requires treatment discontinuation, with exceptions as noted in Section 4.5.5.

4.5.4.2 Criteria to Resume Ipilimumab Dosing

Subjects may resume treatment with nivolumab and 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 4.5.5) 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 BMS Medical Monitor. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
- Dose delay of ipilimumab which results in no ipilimumab dosing for > 12 weeks requires ipilimumab discontinuation, with exceptions as noted in Section 4.5.5.
- Ipilimumab may not be resumed sooner than 6 weeks (+/- 5days) 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 BMS Medical Monitor should be consulted prior to resuming nivolumab in such subjects.

4.5.4.3 Criteria to Resume Treatment with Chemotherapy

- Subjects may resume treatment with chemotherapy when the ANC returns to 1500/µl, the platelet count returns to 100,000/mm3, 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 re-treatment, then re-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 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 chemotherapy treatment, please follow the dose reduction recommendations in Section 4.5.3.2.

4.5.5 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. Tumor assessments for subjects who discontinue study treatment without radiographic progression, confirmed by independent radiology review (Section 7.2), should continue as per protocol until radiographic progression is determined by blinded independent central review.

Part 2: If a subject is intolerant of nivolumab treatment during the chemotherapy cycles, the subject should be withdrawn from the study.

Chemotherapy dose reduction is allowed on study. Any subject with two prior dose reductions to one agent who experiences a toxicity that would cause a third dose reduction must be discontinued from that agent. A subject in treatment arm who is discontinued from the chemotherapy treatment will remain on the study and receive nivolumab and ipilimumab therapy with option of pemetrexed maintenance (non-squamous histology only).

If the investigator assesses the drug-related AE to be related to ipilimumab only and not related to nivolumab, ipilimumab dosing alone may be discontinued while nivolumab dosing is delayed until the subject meets criteria to resume nivolumab treatment.

4.5.5.1 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 re-treatment period OR requires systemic treatment
- Any Grade ≥ 2 drug-related pneumonitis or interstitial lung disease that does not resolve to dose delay and systemic steroids (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 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reactions, infusion reactions, endocrinopathies, and laboratory abnormalities
- Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, myocarditis, 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. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement

- 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):
- Any drug related liver function test (LFT) abnormality that meets the following criteria require discontinuation
  - Grade ≥ 3 drug-related AST, ALT or Total Bilirubin requires discontinuation*

    * In most cases of Grade 3 AST or ALT elevation, study drugs(s) will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drugs(s), a discussion between the investigator and the BMS medical monitor or designee must occur.
  - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2x 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 BMS 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 hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor.
  - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor. Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks, the BMS 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 meets criteria for discontinuation and investigator is unable to determine whether the event is related to nivolumab, ipilimumab or chemotherapy (if chemotherapy is part of the treatment regimen), the subject should discontinue nivolumab, ipilimumab and chemotherapy (if chemotherapy is part of the treatment regimen), and be taken off the treatment phase of the study. Continuation of ipilimumab after discontinuation of nivolumab is not allowed on study. The assessment for discontinuation of nivolumab and ipilimumab should be made separately from the assessment made for discontinuation of chemotherapy doublet. If criteria for discontinuation for nivolumab and ipilimumab are met before the nivolumab and ipilimumab plus platinum doublet chemotherapy cycles have been completed, platinum doublet chemotherapy may continue until 2 cycles have been given in Part 2 study.

4.5.5.2 Definition of DLTs in safety-lead in of Part 2

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

- Any Grade 2 drug-related uveitis or eye pain that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 2 drug-related pneumonitis or interstitial lung disease that does not resolve to dose delay and systemic steroids in 14 days (radiologic changes may take longer to resolve). The management algorithm for pneumonitis or pulmonary toxicity can be found in the appendix and in the current Investigator Brochure.[22]
- Any Grade 3 non-skin drug-related adverse event with the exception of laboratory abnormalities, that cannot be alleviated (defined as returning to grade 1, radiologic changes may take longer to resolve) or controlled by appropriate care within 14 days (appropriate care being defined as treatment outlined in AE management algorithms in the investigators brochure).
- Any Grade 4 drug-related adverse event including laboratory abnormalities except Grade 4 leukopenia or neutropenia lasting < 14 days and asymptomatic amylase/lipase evaluation.
- Any of the following drug-related hepatic function laboratory abnormalities:
  - AST or ALT > 5-10x 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
  - Grade 3 thrombocytopenia associated with bleeding

  Safety lead in subjects should discontinue treatment if they experience any adverse event, laboratory abnormality or intercurrent illness (regardless of causality) which, in the opinion of the investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing. Such discontinuation, however, will not be considered a DLT unless it meets at least one of the DLT criteria defined above. Treatment delay, modification, and discontinuation criteria are to be followed for management of safety lead in subjects as outlined in Sections 4.5.2, 4.5.3, 4.5.5.

4.5.5.3 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:
  - Grade ≥ 3 drug related AST, ALT or Total Bilirubin required discontinuation
    - In most cases of Grade 3 AST, ALT evaluation study drug(s) will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug(s), a discussion between the investigator and the BMS medical monitor or designee must occur.
  - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2X 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.
  - 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 BMS 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 BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.
- Dosing delays resulting in no ipilimumab dosing for > 12 weeks that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor. Prior to re-initiating treatment in a subject with a dosing delay lasting > 12 weeks, the BMS 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 ipilimumab 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 meets criteria for discontinuation and investigator is unable to determine whether the event is related to nivolumab, ipilimumab or chemotherapy (if chemotherapy is part of the treatment regimen), the subject should discontinue nivolumab, ipilimumab or chemotherapy (if chemotherapy is part of the treatment regimen) and be taken off the treatment phase of the study. The assessment for discontinuation of nivolumab and ipilimumab should be made separately from the assessment made for discontinuation of chemotherapy doublet. If criteria for discontinuation for nivolumab and ipilimumab are met before the nivolumab and ipilimumab plus platinum doublet chemotherapy cycles have been completed, platinum doublet chemotherapy may continue until 2 cycles have been given in Part 2 study.

4.5.5.4 Chemotherapy Dose Discontinuation

Except where specified below, chemotherapy drugs in the platinum doublet chemotherapy regimen or pemetrexed should be discontinued for any of the following:

- Any Grade ≥ 3 peripheral neuropathy
- Grade ≥ 3 drug-related thrombocytopenia associated with clinically significant bleeding
- Any drug-related liver function test (LFT) abnormality that meets the following criteria requires discontinuation:
  - AST or ALT > 5-10x ULN for > 2 weeks
  - AST or ALT > 10x ULN
  - Total bilirubin > 5 x ULN
  - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Any drug-related adverse event which recurs after two prior dose reductions for the same drug-related adverse event 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 BMS medical monitor. Prior to re-initiating

treatment in a subject with a dosing delay lasting > 6 weeks, the BMS 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.
- In addition, subjects receiving cisplatin with pemetrexed must discontinue cisplatin if the calculated creatinine clearance decreases to < 50 mL/min based on the Cockcroft Gault formula) The other drug (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 when the subject meets retreatment criteria.

Note: If the investigator is unable to determine whether an adverse event is due to nivolumab or ipilimumab or platinum doublet chemotherapy, then all drugs must be discontinued. The assessment for discontinuation of nivolumab and ipilimumab should be made separately from the assessment made for discontinuation of chemotherapy doublet. If criteria for discontinuation for nivolumab and ipilimumab are met before the nivolumab and ipilimumab plus platinum doublet chemotherapy cycles have been completed, platinum doublet chemotherapy may continue until 2 cycles have been given in Part 2 study.

A subject who is discontinued from the chemotherapy treatment due to toxicities related to chemotherapy only, will remain on the study and receive nivolumab and ipilimumab therapy.

4.5.6 Treatment Beyond Disease Progression for Part 1 and Part 2

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[21]

Subjects will be permitted to continue on nivolumab + ipilimumab for treatment beyond initial RECIST 1.1 defined PD, assessed by the investigator, for a maximum of 2 years from the start of study treatment as long as they meet the following criteria:

- Investigator-assessed clinical benefit and no rapid disease progression
- Subject is tolerating study 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 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 should be discussed with the BMS Medical Monitor and documented in the study records. A follow-up scan should be performed within six (6) weeks ± 5 days of original PD to determine whether there has

been a decrease in the tumor size, or continued progression of disease. Subsequent scans should be performed per protocol defined schedule ± 5 days until further progression is determined.

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 and Table 5.1-3.

For the subjects who continue study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden with a minimum of 5 mm absolute increase 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 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 measureable and therefore included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). 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.

4.5.7 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
- Endocrinopathy
- Skin
- Neurological

[redacted]

4.5.8 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 BMS Medical Monitor and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE (Version 4.0) guidelines.

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

For Grade 1 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 of Study Drug

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

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

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

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

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

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

4.9 Return of Study Drug

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

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

Arrangements for the return of study drug will be made by the responsible Study Monitor.

4.10 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 Assessments and Procedures (CA209568) - All Subjects

Procedure	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	Section 2.3
Inclusion/Exclusion Criteria	X	Section 3.3. All inclusion/exclusion criteria should be assessed prior to first dose
Medical History	X	Section 3.3 and 5.3
Safety Assessments		
Physical Measurements/Physical Examination	X	Section 5.3. Include Height and Weight. Within 28 days prior to first dose
ECOG Performance Status	X	Section 5.3.1 and Appendix 1
Vital Signs and Oxygen Saturation	X	Section 5.3 Including BP, HR, & temperature. Obtain at the screening visit and within 72 hours prior to first dose
Assessment of Baseline Signs and Symptoms	X	Section 5.3 Within 14 days prior to first dose
Concomitant Medication Collection	X	Section 3.4 Within 14 days prior to first dose through the study treatment period
Pregnancy Test (WOCBP only)	X	Section 5.3.2 Within 24 hours prior to Day 1/Negative pregnancy test required at Screening. (An extension up to 72 hours prior to start of study drug may be permissible in situations where results cannot be obtained within the standard 24 hour window).

Table 5.1-1: Screening Assessments and Procedures (CA209568) - All Subjects

Procedure	Screening Visit	Notes
Laboratory Tests	X	Section 5.3 CBC w/differential, Chemistry panel including: LDH, AST, ALT, ALP, T. bili, BUN or serum urea level, creatinine, albumin, Ca, Mg, Na, K, Cl, phosphate, glucose, amylase, lipase, TSH, Free T4, Free T3, within 14 days prior to first dose. Hep B/C (HBV sAg, HCV antibody or HCV RNA), within 28 days prior to first dose.
ECG (12-lead)	X	Section 5.3.4 Obtained only for subjects who have met all eligibility criteria
Efficacy Assessments		
Radiographic Tumor Assessments(chest, abdomen, pelvis, brain)	X	Section 5.4 Performed within 28 days prior to first dose. CT of chest, abdomen and pelvis, and MRI of brain (to rule out brain metastases) & all known or suspected sites of disease should be assessed at baseline
Biomarker Assessments		
Archived Tumor Tissue or Recent Tumor Biopsy	X	Section 3.3.1 Recent sample or archival, obtained within 6 months of Part 1 enrollment (archival tissue is to be obtained within 3 month prior to Part 2 enrollment). One (1) formalin-fixed paraffin embedded tumor tissue block or a minimum of 10 unstained tumor tissue sections are acceptable. Submission of fewer than 10 unstained slides may be acceptable in some circumstances following discussion with the BMS Medical Monitor. Specimens must be tested by third party lab to determine PD-L1 status. An email or fax communication will be sent to site by third party lab for confirmation upon receiving tumor tissue. Subjects in Part 1can initiate therapy before the result of IHC testing. Subjects in safety lead in phase can initiate therapy before the result of IHC test.

Table 5.1-1: Screening Assessments and Procedures (CA209568) - All Subjects

Procedure	Screening Visit	Notes
EGFR Mutation ALK Translocation Status	X	Section 3.3.2 To be performed prior to first dose for all non-squamous subjects. EGFR and ALK tests are to be done locally (not by central lab). EGFR test is mandatory for subjects with non-squamous histology, and to be performed using PCR based assay or next generation sequencing from tumor tissue. Tests other than PCR or next generation sequencing will be requested to repeat using PCR or next generation sequencing based methods.
IWRS /Clinical Drug Supplies		
IWRS	X	Section 4.4 For subject number assignment at the time informed consent is obtained

Table 5.1-2: On Study Assessments Treatment Phase (CA209568) Part 1 (2 weeks/cycle)					
Part 1 Procedure[a]	**Cycle 1 Day 1**	**Each Subsequent Cycle Day1** (± 3 Days)	**Every 2 Cycles Day 1** (± 3 Days)	**Every 3 Cycles Day 1** (± 3 Days)	**Notes For purposes of this table, a cycle refers to the nivolumab every 2 weeks regimen.**
Safety Assessments					
Physical Measurements & ECOG Performance Status	X	X			Section 5.3, 5.3.1 & Appendix 1
Vital Signs and Oxygen Saturation	X	X			Section 5.3
Adverse Event Assessments	Continuously during the study				Section 6. SAEs should be approved in Trial Access Online (TAO) within 5 days from entry. Beyond 100 days from the last dose of study drug, subjects will be followed for ongoing drug-related adverse events until resolved, return to baseline or deemed irreversible, or until lost to follow-up, withdrawal of study consent, or start of subsequent therapy
[redacted]	[redacted]	[redacted]			[redacted]
Laboratory Tests	X	X		X (TSH)	Section 5.3 Within 72 hrs. prior to dosing to include CBC w/ differential, AST, ALT, ALP, T. bili, BUN or serum urea level, creatinine, albumin, Ca, Mg, Na, K, Cl, LDH, phosphate, glucose, amylase, lipase, TSH (with reflexive Free T4 and Free T3). Thyroid Function Testing to be evaluated every 6 weeks **Note:** C1D1 labs do not need to be repeated if they were performed within 14 days of dosing.
Pregnancy Test (WOCBP only)	X		X		Sections 5.3.2 To be evaluated at least every 4 weeks.

Table 5.1-2: On Study Assessments Treatment Phase (CA209568) Part 1 (2 weeks/cycle)

Part 1 Procedure[a]	Cycle 1 Day 1	Each Subsequent Cycle Day1 (± 3 Days)	Every 2 Cycles Day 1 (± 3 Days)	Every 3 Cycles Day 1 (± 3 Days)	Notes For purposes of this table, a cycle refers to the nivolumab every 2 weeks regimen.
Efficacy Assessments					
Radiographic Tumor Assessment (CT of chest, abdomen and pelvis)	Section 5.4. **FIRST** tumor assessment should first be performed at 6 weeks (± 7 days) from first dose date. **SUBSEQUENT** tumor assessments should occur every 6 weeks (± 7 days) up to first 12 months (week 48), then every 12 weeks until disease progression. Tumor assessments' should continue when maximum 2 years of therapy is reached. . *Subjects with a history of brain metastasis may have surveillance MRI approximately every 12 weeks from the date of first dose, or sooner if clinically indicated.				
[redacted]					
[redacted]	[redacted]				[redacted]
[redacted]					
[redacted]		[redacted]			[redacted]
[redacted]		[redacted]			[redacted]
Clinical Drug Supplies					
IWRS Vial Assignment	X	X			Section 4.4. Within 3 business days prior to first dosing
Nivolumab 3 mg/kg q 2 weeks + Ipilimumab 1 mg/kg q 6 weeks [b]	X	X			Section 4.5 & Table 4.5-1

[a] If a dose is delayed, the procedures scheduled for that same time point should be delayed to coincide with when the time point's dosing actually occur (except radiographic tumor assessments).

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

Table 5.1-3: On Study Assessments Treatment Phase-
Part 2 - Nivolumab+ ipilimumab+ platinum-doublet chemotherapy combination (3 weeks/cycle)

Part 2 Procedure	Cycle 1 Day 1	Each Subsequent Cycle Day1 (± 3 Days)	Every 2 Cycles Day 1 (± 3 Days)	Every 3 Cycles Day 1 (± 3 Days)	Notes For the purposes of this table, a cycle refers to the nivolumab +ipilimumab+ platinum-doublet chemotherapy every 3 weeks x2 cycles regimen
Safety Assessments					
Physical Measurements & ECOG Performance Status	X	X			Sections 5.3, 5.3.1 Appendix 1
Vital Signs and Oxygen Saturation		X			Section 5.3
Adverse Event Assessments	Continuously during the study				Section 6. SAEs should be approved in Trial Access Online (TAO) within 5 days from entry.
[redacted]	[redacted]	[redacted]			[redacted]
Laboratory Tests	X	X	X(TSH)		Section 5.3 Within 72 hrs. prior to dosing to include CBC w/ differential, AST, ALT, ALP, T. bili, BUN or serum urea level, creatinine, albumin, Ca, Mg, Na, K, Cl, LDH, phosphate, glucose, amylase, lipase, TSH (with reflexive Free T4 and Free T3). Thyroid Function Testing to be evaluated every 6 weeks **Note:** C1D1 labs do not need to be repeated if they were performed within 14 days of dosing.
Pregnancy Test (WOCBP only)	X	X			Sections 5.3.2 To be evaluated at least every 3 weeks for cycles 1- 4 and a minimum of every 4 weeks after cycle 4 dose, to align with clinic visits.
Efficacy Assessments					
Radiographic Tumor Assessment (CT/MRI chest, abdomen, pelvis)	**Section 5.4.** **FIRST** tumor assessment should first be performed at 6 weeks (± 7 days) from first dose date.				

**Table 5.1-3: On Study Assessments Treatment Phase-
Part 2 - Nivolumab+ ipilimumab+ platinum-doublet chemotherapy combination (3 weeks/cycle)**

Part 2 Procedure	Cycle 1 Day 1	Each Subsequent Cycle Day1 (± 3 Days)	Every 2 Cycles Day 1 (± 3 Days)	Every 3 Cycles Day 1 (± 3 Days)	Notes For the purposes of this table, a cycle refers to the nivolumab +ipilimumab+ platinum-doublet chemotherapy every 3 weeks x2 cycles regimen
	SUBSEQUENT tumor assessments should occur every 6 weeks (± 7 days) up to first 12 months (week 48), then every 12 weeks until disease progression. Tumor assessments should continue after maximum 2 years of treatment is reached. * Subjects with a history of brain metastasis may have surveillance MRI approximately every 12 weeks from the date of first dose, or sooner if clinically indicated.				
Optional Tumor Biopsy for Gene Expression Profiling	X				Section 5.6.2.6. As feasible obtained at baseline or any time on treatment
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

**Table 5.1-3: On Study Assessments Treatment Phase-
Part 2 - Nivolumab+ ipilimumab+ platinum-doublet chemotherapy combination (3 weeks/cycle)**

Part 2 Procedure	Cycle 1 Day 1	Each Subsequent Cycle Day1 (± 3 Days)	Every 2 Cycles Day 1 (± 3 Days)	Every 3 Cycles Day 1 (± 3 Days)	Notes For the purposes of this table, a cycle refers to the nivolumab +ipilimumab+ platinum-doublet chemotherapy every 3 weeks x2 cycles regimen
Clinical Drug Supplies					
IWRS Vial Assignment	X	X			Section 4.4. Within 3 business days prior to first dosing
Nivolumab + ipilimumab + platinum-doublet chemotherapy q 3w x2 cycles	X	X			Section 4.5 & Table 4.5-2

Note: If a dose is delayed, the procedures scheduled for that same time point should be delayed to coincide with when the time point's dosing actually occur (except radiographic tumor assessments) continue until disease progression, discontinuation due to unacceptable toxicity, withdrawal of consent, or study closure

Table 5.1-4: Follow-up and Survival Procedures (CA209568) - All subjects

Procedure	Follow-Up Visits 1 & 2[a]	Survival Follow-up Visits[b]	Notes
SAFETY ASSESSMENTS			
Targeted Physical Examination	X		Section 5.3. To assess for potential late emergent study drug related issues.
Vital Signs	X		Section 5.3.
Adverse Event Assessment	X	X	Section 6. SAEs should be approved in Trial Access Online (TAO) within 5 days from entry.
[redacted]	[redacted]		[redacted]
Laboratory Tests	X		Section 5.3. Required at Visit 1. Repeat at Visit 2 only if study drug related toxicity persists.
Pregnancy Test (WOCBP only)	X		Section 5.3.2.
EFFICACY ASSESSMENTS			
Radiographic Tumor Assessment (CT of chest, abdomen and pelvis and known sites of disease)	X	X	Section 5.4. For subjects who discontinue study treatment for reasons other than PD, follow up scans should be performed every 6 weeks (± 1 wk) up to first 12 months (week 48), then every 12 weeks until PD, lost to follow-up, or withdrawal of consent. *Radiographic assessments for subjects who have not experienced PD ***must*** be obtained every 6 weeks (± 7 days), and ***not*** delayed until follow-up visits 1 & 2.
[redacted]	[redacted]	[redacted]	[redacted]
Collection of Survival Status and Subsequent Therapy Information	X	X	Section 3.6. Collect **every 3 months** in Survival Visits until death, lost to follow-up, or withdrawal of study consent. May be performed by phone contact or office visit.

[a] Follow-Up Visit 1 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 to occur 115 days from Follow-Up Visit 1 (± 7 days).

[b] Survival Follow-Up Visits to occur approximately every 3 months from Follow-Up Visit 2.

[c] For Part 2 subjects only

5.1.1 Retesting During Screening or Lead-in Period

Retesting of laboratory parameters and/or other assessments during the Screening period will not be permitted (this does not include parameters that require a confirmatory result).

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

5.2 Study Materials

- NCI CTCAE version 4
- Nivolumab Investigator Brochure
- Ipilimumab Investigator Brochure
- Pharmacy Binder
- Laboratory manuals for collection and handling of blood (including PK, biomarker and immunogenicity) and tissue specimens
- Site manual for operation of Interactive Web Response System (IWRS), including enrollment worksheets
- Manual for entry of local laboratory data
- Pregnancy Surveillance Forms
- RECIST 1.1 pocket guide
- CA209568 study Imaging Manual
- Blinded Independent Central Review manual
- [redacted]

5.3 Safety Assessments

At baseline, a medical history will be obtained to capture relevant underlying conditions. The baseline examinations should include weight, height, ECOG Performance Status, blood pressure (BP), heart rate (HR), and temperature at rest, and should be performed within 28 days prior to first dose. Baseline signs and symptoms are those that are assessed within 14 days prior to first dose. Concomitant medications will be collected from within 14 days prior to the first dose through the study treatment period (see Section 5.1).

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

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

Pregnancy testing for WOCBP (done locally) must be performed within 24 hours prior to the Day 1 at baseline and then every 4 weeks (2 cycles) ± 3 days. Pregnancy testing must be within 24 hours prior to Day 1 of each treatment cycle (prior to dosing).

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

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 4.0.

On-study weight, ECOG performance status, 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. The start and stop time of the study therapy infusions 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 treatment local laboratory assessments are to be completed within 72 hours prior to dosing.

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 participant shows pulmonary-related signs (hypoxia, fever) or symptoms (eg. dyspnea, cough, fever) consistent with possible pulmonary adverse events, the participant should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm in the BMS-936558 (nivolumab) Investigator Brochure.

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 ECOG Performance Status

Eastern Cooperative Oncology Group (ECOG) Performance Status will be evaluated and documented at Screening and within 72 hours prior to each dosing visit as outlined in Section 5.1. See **Appendix 1** for description of ECOG status.

5.3.2 Pregnancy Testing

WOCBP are required to have pregnancy tests performed. WOCBP must exhibit a negative serum or urine pregnancy (minimum sensitivity 25 IU/L or equivalent units of HCG within 24 hours prior to Day 1 of each treatment period and safety follow-up visits. Pregnancy testing will be done locally and as outlined in Section 5.1. An extension up to 72 hours prior to start of study drug may

be permissible in situations where results cannot be obtained within the standard 24 hour window. This is subject to medical monitor/MST Chair approval.

5.3.3 Thyroid Function Testing

Thyroid function testing will be performed as outlined in Section 5.1

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** of the protocol.

5.3.4 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

Images will be submitted to an imaging third party radiology vendor for central review (for subjects participating in Part 1). Any additional imaging that may demonstrate tumor response or progression (including scans performed at unscheduled timepoints and/or at an outside institution) should be collected for RECIST 1.1 tumor assessment and submitted to the BICR. Sites will be trained prior to scanning the first study subject. Image acquisition guidelines and submission process will be outlined in the study Imaging Manual to be provided by the radiology vendor. 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 a Blinded Independent Central Review from the third party radiology vendor for confirmation of progression, as specified in Section 7.2.

Contrast enhanced CT with PO/IV 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, local prophylaxis standards may be used to obtain the assessment with contrast if at all possible, or use the alternate modality. In cases where contrast is strictly contraindicated, a non-contrast scan will suffice. Should a subject have a contraindication for CT IV contrast, a non-contrast CT of the chest and a contrast enhanced MRI of the abdomen and pelvis may be obtained. Every attempt should be made to image each subject using an identical acquisition protocol on the same scanner for all imaging time points. (Applies to both Part 1 and Part 2 Safety Lead in).

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 IV and oral contrast) then

the CT portion of the FDG-PET/CT can be used for RECIST 1.1measurements. 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 required at screening in order to rule out active metastatic disease.

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 first dose. In addition to the chest, abdomen, pelvis, and brain (to rule out 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 at week 6 (± 7 days) from first dose date, then every 6 weeks (± 7 days) for the first 12 months (until week 48) and every 12 weeks (± 7 days) thereafter, until disease progression is documented or treatment is discontinued (whichever occurs later). Subjects with a history of brain metastasis may have surveillance MRI approximately every 12 weeks from the date of first dose, or sooner if clinically indicated.

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 3.

Tumor assessments should be submitted to the third party radiology vendor as they are performed on an ongoing basis, with the exception of safety lead in subjects. At the time of investigator-assessed disease progression, the site must request a Blinded Independent Central Review from the third party radiology vendor, as specified in Section 7.2.

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 ipilimumab +/- chemotherapy 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 Blinded Independent Central Review. Subjects who start palliative local therapy or subsequent therapy without prior assessment of RECIST 1.1 progression by central review, the Blinded Independent Central Review 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 Blinded Independent Central Review 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

Part 1: The primary endpoint is objective response rate (ORR) based on blinded independent central review assessment in all treated PD-L1 positive (≥ 1%) subjects and ORR in all treated PD-L1 negative (< 1%) subjects. All treated subjects will be monitored by radiographic assessment every 6 weeks (± 7 days) until week 48 and every 12 weeks (± 7 days) thereafter [beginning from the first on-study assessment on week 6 (± 7 days)], to determine changes in tumor size. RECIST 1.1 criteria will be used for the assessment.

Part 2:

Primary Endpoints will be descriptive.

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

5.4.2 Secondary Efficacy Assessment

Part 1: Objective response rate (ORR) based on blinded independent central review assessment in all treated subjects. Progression free survival (PFS) based on blinded independent central review assessment, overall survival and ORR, PFS and OS by PD-L1 expression levels.

Part 2:

- ORR, PFS by investigator assessment, and OS

[redacted]

[redacted]

[redacted]

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.)

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.

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 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 100 days of discontinuation of dosing. For subjects randomized to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of treatment. 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 BMS (or designee) within 24 hours of awareness of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. 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 BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

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

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

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

6.3 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 BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy.

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

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

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

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

6.5 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:

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

6.7 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. This list is subject to change based on Health Authority feedback or change of MedDRA version. The final list used will be described in the CSR.

Table 6.7.1-1 below provides a summary of the IMAEs category and their respective PTs. This list is subject to change based on Health Authority feedback or change of MedDRA version. The final list used will be described in the CSR.

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 Health Authorities for review on a specified timeframe in accordance with the adjudication documentation.

7.1 Data Monitoring Committee (DMC)

Not applicable.

7.2 Blinded Independent Radiology Central Review

At the time of investigator-assessed initial radiographic progression per RECIST 1.1 in any given subject, the site must request the Independent Central Review from the third party radiology vendor for confirmation of progression for Part 1.

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.

The Blinded Independent Central Review will also review tumor images in all treated subjects (Part 1) to determine RECIST 1.1 response for the analyses of ORR or PFS. Details of the Blinded Independent Central Review responsibilities and procedures will be specified in the Blinded Independent Central Review charter.

At time of analysis of ORR or PFS, Independent Radiology Review Committee will review tumor assessments in all treated subjects to determine RECIST 1.1 progression and response for the analyses of PFS and ORR. Details of the IRRC responsibilities and procedures will be specified in the IRRC charter.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

The reported objective response rate for the investigational treatment based on 77 treated subjects treated with nivolumab plus ipilimumab in phase I study CA209012 was 43% in August 2015-database lock. The reported objective response rate based on 23 PD-L1 positive subjects was 48%. However, given the small sample size in that cohort, the observed ORR in CA209568 might be lower.

Table 8.1-1 summarizes the 95% exact CI for some scenarios of observed ORRs and 95% confidence intervals. The part 1 sample size of at least 120 PD-L1 positive subjects, can provide 95% confidence that the observed ORR can be estimated to within 9.5% of the estimates. With an observed ORR of 48%, the lower bound of the observed ORR is not less than 39%. In addition, the 95% exact CI for the target ORRs for a sample size of 60 PD-L1 ≥50% population and 100 PD-L1 negative subjects are summarized. The sample sizes of approximately 300 all treated subjects, 60 PD-L1 ≥ 50% subjects and 100 PD-L1 negative subjects, can provide 95% confidence that the observed ORR can be estimated to within 5.8%, 13.5% and 10.5% of the estimates.

Table 8.1-1: Observed ORR with Exact 95% CI

ORR	# Responders	95% Exact CI
N=300 All Treated		
30%	90	[24.9, 35.5]
40%	120	[34.4, 45.8]
50%	150	[44.2, 55.8]
N=120 PD-L1 positive		
40%	48	[31.2; 49.3]
44%	53	[35.1; 53.5]
48%	58	[39.1; 57.6]
57.5%	69	[48.1, 66.5]
N=60 PD-L1 ≥ 50%		
60%	36	[46.5; 72.4]
65%	39	[51.6; 76.9]
70%	42	[56.8; 81.2]
N=100 PD-L1 negative		
10%	10	[4.9, 17.6]
20%	20	[12.7, 29.2]
30%	30	[21.2, 40.0]
40%	40	[30.3, 50.3]

95% CI based on Clopper-Pearson method

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

For Part 2 lead-in phase, there are 22 DLT evaluable subjects within 28 subjects who initiate treatment assuming 20% of subjects do not complete the 9 week DLT evaluation period for reasons other than dose limiting toxicities. With a sample size of 22 DLT evaluable subjects with a safety event incident rate as 10%, there is above 90% probability to observe 1 or more cases of this safety event in this group. The goal is to identify safe regimens for future development, and safe is defined as 25% evaluated subjects or less exhibit DLTs (ie, 5 or less subjects with such events out of 22 subjects). With 22 evaluable subjects, the false rejection rate is 10% if the true toxicity rate is 15%, the false acceptance rate is 16% if the true toxicity rate is 35%. The false rejection and false acceptance rates are deemed acceptable.

8.2 Populations for Analyses

Part 1:

- All enrolled subjects: all subjects who signed an informed consent form and were registered into the IWRS

- All treated subjects: all subjects who received at least one dose of any study medication.
- All treated PD-L1 positive subjects: all treated subjects with PD-L1 membranous staining in ≥ 1% tumor cells.
- All treated PD-L1 negative subjects: all treated subjects with PD-L1 membranous staining in < 1% tumor cells.
- All Treated PD-L1 ≥ 50% subjects: all treated subjects with PD-L1 membranous staining in ≥ 50% tumor cells). This is a subject set of subjects in all treated PD-L1 positive subjects.

Part 2:

- All enrolled subjects: all subjects who signed an informed consent form and were registered into the IWRS
- All treated subjects: all subjects who received at least one dose of any study medication. This is the primary dataset for dosing and safety analysis.

Safety lead in subjects will be described separately on safety and efficacy (ie overall response rate and DLT incidence).

Additional specific populations will be described in the statistical analysis plan

8.3 Endpoints

8.3.1 Primary Endpoint(s)

Part 1:

- ORR in all treated PD-L1 positive (≥ 1%) subjects by blinded independent central review per RECIST 1.1 in stage IV NSCLC subjects with nivolumab in combination with ipilimumab as first line therapy.
- ORR in all treated PD-L1 negative (< 1%) subjects by blinded independent central review per RECIST 1.1 in stage IV NSCLC subjects treated with nivolumab in combination with ipilimumab as first line therapy.

ORR is defined as the number of subjects with a best overall response (BOR) of confirmed CR or PR divided by the number of treated subjects. BOR is defined as the best response designation, as determined by the blinded independent central review, recorded between baseline and the date of objectively documented progression per RECIST 1.1 or the date of initiation of palliative local therapy or the date of initiation of subsequent anticancer therapy, whichever occurs first. For subjects without documented progression or palliative local therapy or subsequent anti-cancer therapy, all available response designations will contribute to the BOR determination. For subjects who continue treatment beyond progression, the BOR will be determined based on response designations recorded up to the time of the initial RECIST 1.1-defined progression.

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

Further characterization of the response will include time to objective response (time from first dosing date to first CR or PR) and depth of response (maximum tumor shrinkage in target lesions).

The analysis of the primary endpoint ORR will be performed at least six month after last subject first treatment.

Part 2:

Primary Endpoints:

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

Safety and tolerability objectives will be measured by the incidence of adverse events, serious events, deaths, and laboratory abnormalities.

8.3.2 Secondary Endpoint(s)

Part 1:

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

Part 2:

- ORR, PFS by investigator assessment, and OS

[redacted]

[redacted]

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Demographics and baseline laboratory results will be summarized using descriptive statistics for all treated subjects in Part 1 and by randomized treatment arm for all randomized subjects in Part 2.

8.4.2 Efficacy Analyses

8.4.2.1 Methods for Primary Endpoints

Among all treated subjects in Part 1, the ORR (based on blinded independent central review assessments) will be summarized by binomial response rates and their corresponding two-sided 95% exact CIs using Clopper-Pearson method. To further characterize the response, time to objective response, depth of response and BOR by response category will be summarized using descriptive statistics.

Among all treated subjects in Part 2, the ORR (based on investigator assessments) will be summarized by binomial response rates and their corresponding two-sided 95% exact CIs using Clopper-Pearson method. To further characterize the response, time to objective response, depth of response and BOR by response category will be summarized using descriptive statistics.

8.4.2.2 Methods for Secondary Endpoints

In parts 1 and 2, separately, time to event distribution such as PFS and OS will be estimated using Kaplan Meier techniques. Median PFS or OS along with 95% CI will be constructed based on a log-log transformed CI for the survivor function. Rates at fixed time points (e.g., PFS at 6 months) will be derived from the Kaplan Meier estimate and corresponding confidence interval will be derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survivor function. ORR, PFS and OS will be assessed by subgroups of PD-L1 expression levels: PD-L1 $\geq$ 50%, PD-L1 positive, PD-L1 negative, PD-L1 not quantifiable.

8.4.3 Safety Analyses

Safety analysis will be performed in all treated subjects. In Part 1, safety analysis will be summarized in PD-L1 positive, PD-L1 negative, and all treated subjects. Part 2 analysis will be performed on all treated subjects. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All on-study AEs, drug related AEs, SAEs and drug-related SAEs, AEs and drug-related AEs leading to drug discontinuation will be tabulated using worst grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term, based on MedDRA terminology. On-study lab parameters including hematology, coagulation, chemistry, liver function and renal function will be summarized using worst grade per NCI CTCAE v 4.0 criteria.

Frequency, management and resolution of IMAEs will be analyzed. A tabular summary of the incidence of overall IMAEs (by preferred term) and serious IMAEs will be performed. A

descriptive analysis of IMAEs including time-to-onset, severity, duration, action taken with the study drug, dosing delays of the study drug, corticosteroid details, re-challenge information and outcome of the AE will be individually characterized by IMAE category (see Section 6.7.1).

Safety lead in subjects will be described separately on safety evaluation.

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

8.5 Interim Analyses

Not applicable

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

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

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

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

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

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

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

9.1.2 Monitoring

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

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

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

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

9.1.2.1 Source Documentation

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered

electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

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

9.1.3 Investigational Site Training

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

9.2 Records

9.2.1 Records Retention

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

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

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

9.2.2 Study Drug Records

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

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- nonstudy disposition (eg, 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.

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

9.2.3 Case Report Forms

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

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used.

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. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

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

9.3 Clinical Study Report and Publications

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

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

- 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. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical

trial agreement (CTA) governing [Study site or Investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to BMS at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	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
ACLS	advanced cardiac life support
AI	accumulation index
AI_AUC	AUC Accumulation Index; ratio of AUC(TAU) at steady state to AUC(TAU) after the first dose
AI_Cmax	Cmax Accumulation Index; ratio of Cmax at steady state to Cmax after the first dose
AI_Ctau	Ctau Accumulation Index; ratio of Ctau at steady state to Ctau after the first dose
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	area under the concentration-time curve
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
AUC(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in one dosing interval
A-V	atrioventricular
β-HCG	beta-human chorionic gonadotrophin
BA/BE	bioavailability/bioequivalence
%BE	percent biliary excretion
BID, bid	bis in die, twice daily
BLQ	below limit of quantification
BMI	body mass index
BMS	Bristol-Myers Squibb
BP	blood pressure
BRt	Total amount recovered in bile

Term	Definition
%BRt	Total percent of administered dose recovered in bile
BUN	blood urea nitrogen
C	Celsius
C12	concentration at 12 hours
C24	concentration at 24 hours
Ca++	calcium
Cavg	average concentration
CBC	complete blood count
Cexpected-tau	expected concentration in a dosing interval
CFR	Code of Federal Regulations
CI	confidence interval
C1-	chloride
CLcr	creatinine clearance
CLD	Dialysate clearance of drug from plasma/serum
CLNR	nonrenal clearance
CLR	renal clearance
CLT	total body clearance
CLT/F (or CLT)	apparent total body clearance
CLT/F/fu or CLT/fu	Apparent clearance of free drug or clearance of free if (if IV)
cm	centimeter
Cmax, CMAX	maximum observed concentration
Cmin, CMIN	trough observed concentration
CNS	Central nervous system
CRC	Clinical Research Center
CRF	Case Report Form, paper or electronic
Ct	Expected concentration at a certain time, usually at the end of an expected future dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
Ctau	Concentration in a dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
Ctrough	Trough observed plasma concentration

Term	Definition
CV	coefficient of variation
CYP	cytochrome p-450
D/C	discontinue
dL	deciliter
DRt	Total amount recovered in dialysate
%DRt	Total percent of administered dose recovered in dialysate
DSM IV	Diagnostic and Statistical Manual of Mental Disorders (4th Edition)
EA	extent of absorption
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEG	electroencephalogram
eg	exempli gratia (for example)
ESR	Expedited Safety Report
F	bioavailability
Fb	fraction of bound drug
FDA	Food and Drug Administration
FI	fluctuation Index ([Cmax-Ctau)/Cavg])
FRt	total amount recovered in feces
%FRt	total percent of administered dose recovered in feces
FSH	follicle stimulating hormone
%FE	percent fecal excretion
fu	fraction of unbound drug
g	gram
GC	gas chromatography
GCP	Good Clinical Practice
G criteria	adjusted R2 value of terminal elimination phase
GGT	gamma-glutamyl transferase
GFR	glomerular filtration rate
h	hour
HBsAg	hepatitis B surface antigen

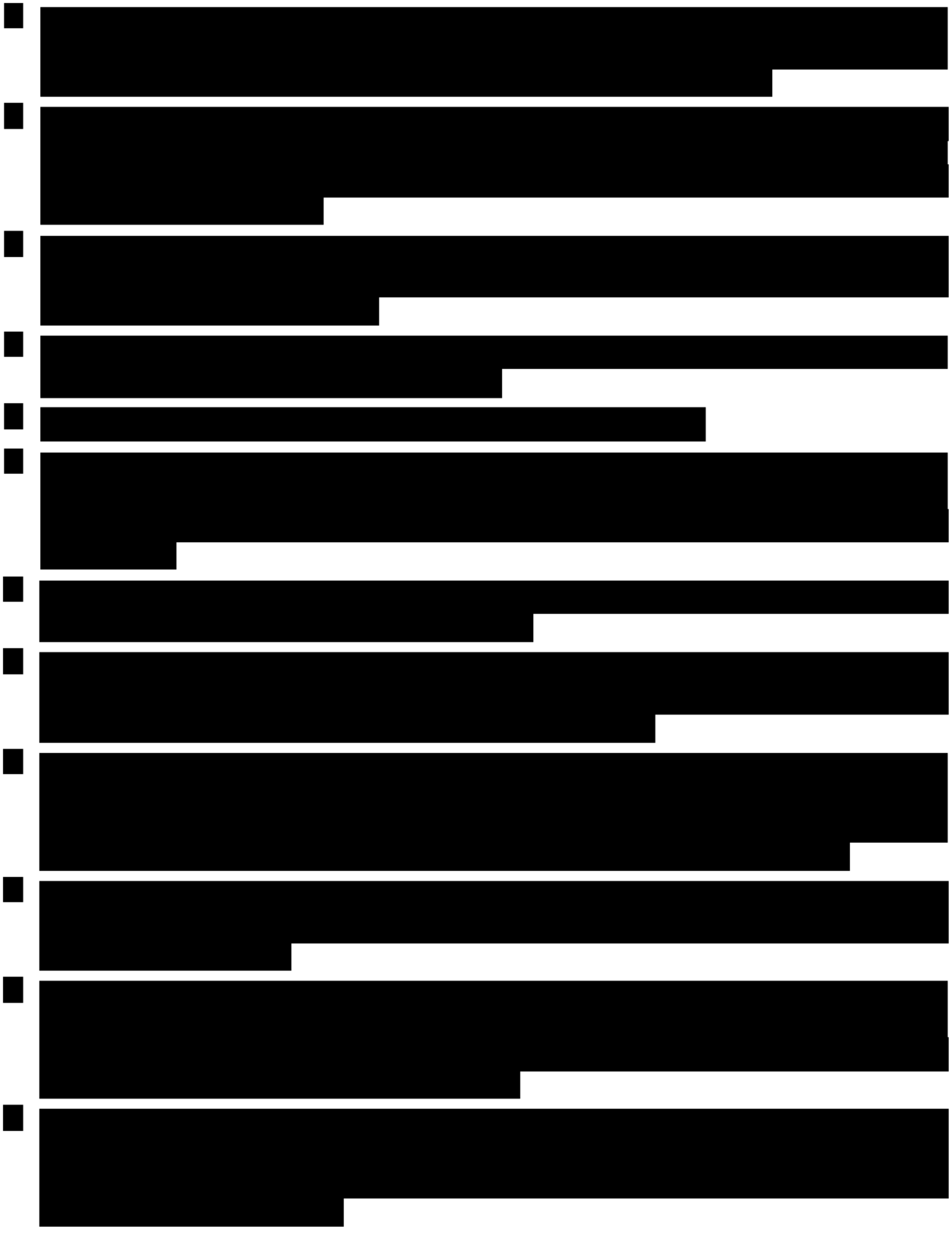
Term	Definition
HBV	hepatitis B virus
HCV	hepatitis C virus
HCO3-	bicarbonate
HIV	Human Immunodeficiency Virus
HR	heart rate
HRT	hormone replacement therapy
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
IRB	Institutional Review Board
IU	International Unit
IV	intravenous
K	slope of the terminal phase of the log concentration-time curve
K3EDTA	potassium ethylenediaminetetraacetic acid
K+	potassium
kg	kilogram
λz	terminal disposition rate constant
L	liter
LAM	Lactation amenorrhea method
LC	liquid chromatography
LDH	lactate dehydrogenase
ln	natural logarithm
Lz_Start	The time point starting the log-linear elimination phase defining the terminal half life
Lz_End	The time point ending the log-linear elimination phase defining the terminal half life
Lz_N	Number of time points in the log-linear elimination phase defining the terminal half life
mg	milligram

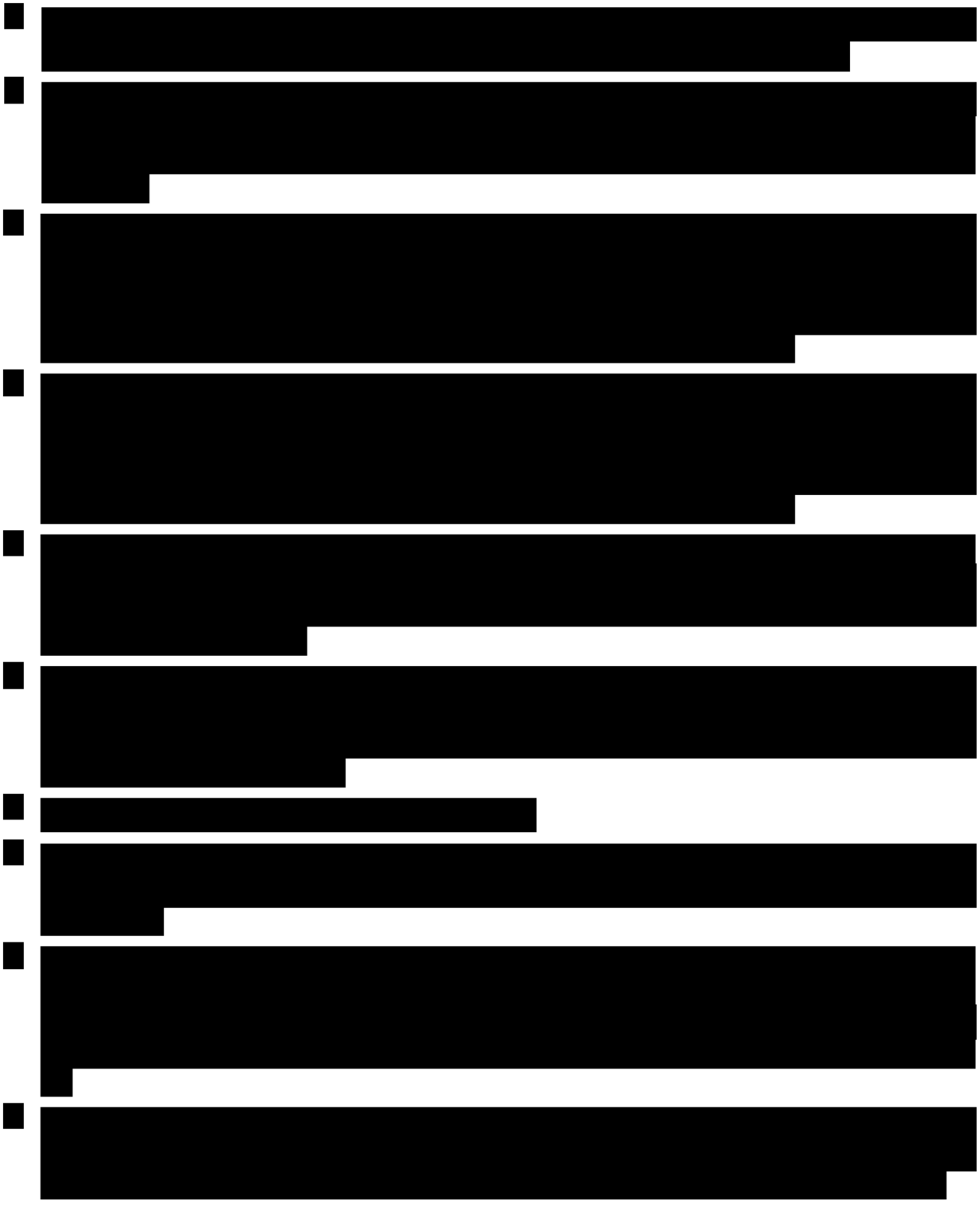
Term	Definition
Mg++	magnesium
MIC	minimum inhibitory concentration
min	minute
mL	milliliter
mmHg	millimeters of mercury
MR_AUC(0-T)	Ratio of metabolite AUC(0-T) to parent AUC(0-T), corrected for molecular weight
MR_AUC(INF)	Ratio of metabolite AUC(INF) to parent AUC(INF), corrected for molecular weight
MR_AUC(TAU)	Ratio of metabolite AUC(TAU) to parent AUC(TAU), corrected for molecular weight
MR_Cmax	Ratio of metabolite Cmax to parent Cmax, corrected for molecular weight
MR_Ctau	Ratio of metabolite Ctau to parent Ctau, corrected for molecular weight
MRT	mean residence time
MS	mass spectrometry
MTD	maximum tolerated dose
µg	microgram
N	number of subjects or observations
Na+	sodium
N/A	not applicable
ng	nanogram
NIMP	non-investigational medicinal products
NSAID	nonsteroidal anti-inflammatory drug
pAUCe	Extrapolated partial AUC from last quantifiable concentration to infinity
Pb	percent of bound drug
PD	pharmacodynamics
PK	pharmacokinetics
PO	per os (by mouth route of administration)
PT	prothrombin time
PTT	partial thromboplastin time
Pu	percent of unbound drug

Term	Definition
QC	quality control
QD, qd	quaque die, once daily
R2	coefficient of determination
RBC	red blood cell
SAE	serious adverse event
SD	standard deviation
SOP	Standard Operating Procedures
sp.	species
Subj	subject
t	temperature
T	time
TAO	Trial Access Online, the BMS implementation of an EDC capability
T-HALF	Half life
T-HALFeff_AUC	Effective elimination half life that explains the degree of AUC accumulation observed
T-HALFeff_Cmax	Effective elimination half life that explains the degree of Cmax accumulation observed)
TID, tid	ter in die, three times a day
Tmax, TMAX	time of maximum observed concentration
TR_AUC(0-T)	AUC(0-T) treatment ratio
TR_AUC(INF)	AUC(INF) treatment ratio
TR_Cmax	Cmax treatment ratio
UR	urinary recovery
%UR	percent urinary recovery
URt	total amount recovered in urine
%URt	total percent of administered dose recovered in urine
UV	ultraviolet
Vss/F (or Vss)	apparent volume of distribution at steady state
Vz	Volume of distribution of terminal phase (if IV and if multi-exponential decline)
W	washout
WBC	white blood cell

Term	Definition
WHO	World Health Organization
WOCBP	women of childbearing potential
x g	times gravity

[redacted]





APPENDIX 1 ECOG PERFORMANCE STATUS

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

[redacted]

APPENDIX 3 RECIST 1.1 GUIDELINES

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:

1. 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
2. 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
3. 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 = unevaluable

[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 duration for SD 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 4 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

[redacted]

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 05		
Section Number & Title	**Description of Change**	[redacted]
Title Page, Synopsis	Change in title	
Synopsis Part 2 description, Part 2 Schema, Section 3.1.2. Study Phase Part 2,	Removal of Part 2 randomization arm	
Synopsis, Primary Objectives Part 2, [redacted] Part 2 Primary Endpoints, Part 2 Secondary Endpoints, [redacted], Section 1.3.1. Primary Objectives Part 2 Primary Endpoints, Secondary Endpoints, Section 3.1.4 Duration of Study Part 2, Section 4.4 Method of Assigning Subject Identification Part 2, Section 4.5.1.2 Part Chemotherapy Dosing Safety Lead-in, Section 4.5.5.4 Chemotherapy Dose Discontinuation. Table 5.1.3, Section 5.4.1 Primary Efficacy Assessment, Section 8.1 Sample Size Determination, Section 8.3.1 Part Primary and Secondary Endpoints, Section 8.4.2 Efficacy Analyses	Removal of Part 2 randomization arm objectives, endpoints, data collection, analyses.	
[redacted] Section 1.5 Overall Risk/Benefit Assessment, Section 3.1 Study Design and Duration, Section 3.2.1.2 Part 2 Study Design,	Safety assessment of DLTs was clarified	
[redacted]	[redacted]	