Official Title of Study:

An Open-Label, Randomized Phase 3 Trial of Nivolumab, or Nivolumab plus Ipilimumab, or Nivolumab plus platinum doublet chemotherapy versus platinum doublet chemotherapy in Subjects with Chemotherapy-Naïve Stage IV or Recurrent Non-Small Cell Lung Cancer (NSCLC)

(CheckMate 227, CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 227)

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Clinical Protocol CA209227

An Open-Label, Randomized Phase 3 Trial of Nivolumab, or Nivolumab plus Ipilimumab, or Nivolumab plus platinum doublet chemotherapy versus platinum doublet chemotherapy in Subjects with Chemotherapy-Naïve Stage IV or Recurrent Non-Small Cell Lung Cancer (NSCLC)

(**CheckMate 227, CHECK**point pathway and nivolu**MA**b clinical **T**rial **E**valuation 227)

Revised Protocol Number: 06
Incorporates Amendment Number 29

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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.

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 06	15-Aug-2018	Incorporates Amendment 29
Amendment 29	15-Aug-2018	Adapt the analyses of Part 2 of CA209227 to evolving science, in order to better demonstrate the benefit of nivolumab plus chemotherapy in subjects with non-squamous histology subtype NSCLC in the first-line setting. The following key changes will be made to the protocol: • The primary endpoint will be evaluated with a hierarchical approach, testing for overall survival (OS) in nivolumab combined with chemotherapy versus chemotherapy alone in subjects with NSCLC of non-squamous histology first, and then in the ITT population. • TMB is incorporated as a secondary endpoint to align with Part 1 of the study, statistical assessments including analysis, and efficacy endpoints have been modified for alignment.
Revised Protocol 05	01-Jun-2018	Incorporates Amendment 25
Amendment 25	01-Jun-2018	Removed OS Interim Analysis from Part 2 and update language for Efficacy Assessments to clarify preferred modality as per Administrative Letter 05.
Administrative Letter 05	05-Apr-2018	To clarify a noted inconsistency in the MRI requirement versus preferred modality for the Brain scan needed for the CA209227 study.
Revised Protocol 04	05-Oct-2017	Incorporates Amendment 19
Amendment 19	05-Oct-2017	Incorporates Tumor Mutational Burden (TMB) update and modified objectives, statistical assessments including analysis, and endpoints for alignment. Rationale also update based on multiple publications across IO as well as post hoc analysis of CA209026 study data.
Revised Protocol 03	27-Jun-2017	Incorporates Amendment 17
Amendment 17	27-Jun-2017	Increased number of enrolled subjects from 739 to 1153 and increased randomized subjects from 480 to approximately 750 for Part 2 only and modified the statistical considerations and sample size justifications accordingly.
Revised Protocol 02	17-Nov-2016	Incorporates Amendment 12
Amendment 12	17-Nov-2016	Modified rationale, objectives, study schema, study design flow chart - time and events schedule, statistical assessments including analysis, endpoints and sample size information for part 1 study design as per revised protocol no. 01, dated 21-Oct-15. Updated rationale, objectives, study schema, flow chart - time and events schedule, investigational products, dosing administration, statistical assessments including analysis, endpoints and sample size information for part 2 study Updated with additional safety and efficacy information from the

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Document	Date of Issue	Summary of Change
		CA209012 study data Updated effective methods of contraception language (section 3.3.1, inclusion criteria) Updated rationale for two year duration of the treatment
Administrative Letter 03	07-Apr-2016	EUDRACT Number was corrected in Administrative Letter 02
Administrative Letter 02	29-Feb-2016	Clarification of contraception
Administrative Letter 01	10-Dec-2015	Minor typographical errors were revised
Revised Protocol 01	21-Oct-2015	Incorporates Amendment 09
Amendment 09	21-Oct-2015	In this document, throughout the protocol, modified text to define PD-L1 +ve NSCLC subjects as 'PD-L1 expressing NSCLC subjects' and PD-L1 -ve NSCLC subjects as 'PD-L1 non-expressing NSCLC subjects' Updated information to drop arm E and add new arm G. Updated rationale, objectives, study schema, flow chart - time and events schedule, dosing administration, dose delays, resume and discontinuation, statistical assessments including analysis, endpoints and sample size information for nivolumab + platinum doublet chemotherapy arm (arm G) Updated with additional safety and efficacy information from the CA209-012 study data Other changes include clarification of the target population, carboplatin dose details when treated with gemcitabine or pemetrexed, clarifications on AST/ALT values when liver mets present, removed CYP3A4 language and typographical revisions throughout the protocol.
Original Protocol	29-May-2015	Not applicable

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SYNOPSIS

Clinical Protocol CA209227

Protocol Title: An Open-Label, Randomized Phase 3 Trial of Nivolumab, or Nivolumab plus Ipilimumab, or Nivolumab plus platinum doublet chemotherapy versus platinum doublet chemotherapy in Subjects with Chemotherapy-Naïve Stage IV or Recurrent Non-Small Cell Lung Cancer (NSCLC)

(CheckMate 227, CHECKpoint pathway and nivolu**MA**b clinical **T**rial **E**valuation 227**)**

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

- Nivolumab (BMS-936558) monotherapy administered IV over 30 minutes at 240 mg every 2 weeks until progression, unacceptable toxicity, or other reasons specified in the protocol, or
- 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, or
- Platinum doublet chemotherapy, based on tumor histology, for up to 4 doses as follows: subjects with squamous histology may receive either gemcitabine (1000 or 1250 mg/m^2) with cisplatin (75 mg/m^2) or gemcitabine (1000 mg/m^2) with carboplatin (AUC 5) or paclitaxel (200 mg/m^2) with carboplatin (AUC 6); subjects with non-squamous histology may receive pemetrexed (500 mg/m^2) with either cisplatin (75 mg/m^2) or carboplatin (AUC 5 or 6); subjects with non-squamous histology may also receive optional continuation maintenance therapy with pemetrexed (500 mg/m^2)
- Nivolumab administered IV over 30 minutes at 360 mg combined with platinum doublet chemotherapy administered IV every 3 weeks up to 4 doses, followed by nivolumab administered IV over 30 minutes at 360 mg every 3 weeks until progression, unacceptable toxicity, or other reasons specified in the protocol

Study Phase: 3

Research Hypothesis:

Part 1

- In chemotherapy-naïve subjects with stage IV or recurrent PD-L1 expressing NSCLC, the administration of nivolumab in combination with ipilimumab will improve overall survival (OS), compared with platinum-doublet chemotherapy
- In chemotherapy-naïve subjects with stage IV or recurrent NSCLC with high tumor mutation burden (TMB) at baseline, the administration of nivolumab in combination with ipilimumab, will improve PFS compared with platinum-doublet chemotherapy.

Part 2

- In chemotherapy-naïve subjects with stage IV or recurrent NSCLC irrespective of PD-L1 expression levels, the administration of nivolumab in combination with platinum-doublet chemotherapy, will improve OS compared with platinum-doublet chemotherapy

Objectives:

Part 1

In subjects with previously untreated stage IV or recurrent NSCLC

Primary:

- Subjects with PD-L1 expressing tumors: To compare overall survival (OS) of nivolumab in combination with ipilimumab (Arm B) to platinum-doublet chemotherapy (Arm C) in subjects whose tumors have ≥ 1% PD-L1 expression

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- Subjects with high baseline tumor mutation burden: To compare progression-free survival (PFS based on Blinded Independent Central Review (BICR) assessment), of nivolumab in combination with ipilimumab (Arms B plus D) to platinum-doublet chemotherapy (Arms C plus F) in subjects with high baseline tumor mutation burden regardless PD-L1 expression level

Secondary:
In subjects with previously untreated stage IV or recurrent NSCLC:

- Subjects depending on tumoral PD-L1 expression (these objectives will be hierarchically tested if the co-primary objective of OS in subjects with PD-L1 expressing tumors is positive):
  - To compare PFS, based on BICR assessment, of nivolumab in combination with platinum-doublet chemotherapy (Arm G), to platinum-doublet chemotherapy (Arm F) in subjects whose tumors do not express PD-L1 (<1%)
  - To compare OS of nivolumab in combination with platinum-doublet chemotherapy (Arm G), to platinum-doublet chemotherapy (Arm F) in subjects whose tumors do not express PD-L1 (<1%)
  - To compare OS of nivolumab monotherapy (Arm A) to platinum-doublet chemotherapy (Arm C) in subjects whose tumors have ≥ 50% PD-L1 expression.

- Subjects with high baseline tumor mutation burden (these objectives will be hierarchically tested if the co-primary objective of PFS in subjects with high TMB tumors is positive):
  - To compare PFS (based on BICR assessment) of nivolumab monotherapy (Arm A) to platinum-doublet chemotherapy (Arm C) in subjects whose tumors have ≥ 1% PD-L1 expression and with high baseline tumor mutation burden
  - To compare OS of nivolumab in combination with ipilimumab (Arms B plus D) to platinum-doublet chemotherapy (Arms C plus F) in subjects with high baseline tumor mutation burden regardless PD-L1 expression level
  - To compare OS of nivolumab (Arm A) to platinum-doublet chemotherapy (Arm C) in subjects whose tumors have ≥ 1% PD-L1 expression and with high baseline tumor mutation burden

Part 2
In subjects with previously untreated stage IV or recurrent NSCLC irrespective of PD-L1 expression levels:

Primary:
- In subjects with non-squamous histology (at randomization as stratified):To compare OS of nivolumab in combination with platinum-doublet chemotherapy (Arm H), to platinum-doublet chemotherapy (Arm I)

Secondary:
- In all randomized subjects (ITT population):
  - To compare OS of nivolumab in combination with platinum-doublet chemotherapy (Arm H), to platinum-doublet chemotherapy (Arm I). (This objective will be hierarchically tested if the primary objective of OS in subjects with non-squamous histology tumors is positive).

The following are also secondary objectives but not part of the hierarchy:.
- In subjects with non-squamous histology:
  - To compare the OS of nivolumab in combination with platinum-doublet chemotherapy (Arm H, among high baseline tumor mutation burden (≥ 10 mut/Mb subgroup
  - To compare the PFS, based on BICR assessment, of nivolumab in combination with platinum-doublet chemotherapy (Arm H), to platinum-doublet chemotherapy (Arm I)
  - To compare the ORR (BICR assessment) of nivolumab in combination with platinum doublet chemotherapy (Arm H), to platinum-doublet chemotherapy (Arm I)

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  - To evaluate efficacy (OS, PFS, and ORR) by PD-L1 expressing levels for nivolumab in combination with platinum-doublet chemotherapy (Arm H) and platinum-doublet chemotherapy (Arm I)
  - To evaluate efficacy (OS, PFS, and ORR) by TMB levels for nivolumab in combination with platinum-doublet chemotherapy (Arm H) and platinum-doublet chemotherapy (Arm I)
- In all randomized subjects (ITT population):
  - In subjects with high baseline tumor mutation burden (≥ 10 mut/Mb): To compare the OS of nivolumab in combination with platinum-doublet chemotherapy (Arm H)
  - To compare the PFS, based on BICR assessment, of nivolumab in combination with platinum-doublet chemotherapy (Arm H), to platinum-doublet chemotherapy (Arm I)
  - To compare the ORR (BICR assessment) of nivolumab in combination with platinum-doublet chemotherapy (Arm H), to platinum-doublet chemotherapy (Arm I)
  - To evaluate efficacy (OS, PFS, and ORR) by PD-L1 expressing levels for nivolumab in combination with platinum-doublet chemotherapy (Arm H) and platinum-doublet chemotherapy (Arm I)
  - To evaluate efficacy (OS, PFS, and ORR) by TMB levels for nivolumab in combination with platinum-doublet chemotherapy (Arm H) and platinum-doublet chemotherapy (Arm I)

Exploratory:
Exploratory objectives are listed in Section 1.4.3 of the protocol.

Study Design: This is an open label, randomized, Phase 3 study in adult (≥ 18 years) male and female subjects, with stage IV or recurrent non-small cell lung cancer, PD-L1 expressing or non-expressing, previously untreated for advanced disease. The study has two parts: Part 1 (Part 1A for subjects with PD-L1 tumors and Part 1B for subjects with PD-L1 non-expressing tumors) and Part 2 for subjects regardless of tumor PD-L1 expression level.

Part 1

Subjects will first be assessed for PD-L1 expression, using 1% cut-off, and categorized into 2 separate groups (PD-L1 expressing and PD-L1 non-expressing). Subjects within each group will be stratified by histology.

- PD-L1 status will be determined by immunohistochemical (IHC) staining of PD-L1 protein in the submitted tumor sample prior to randomization.
  - PD-L1 expressing (≥ 1% tumor cell membrane staining in a minimum of a hundred evaluable tumor cells) vs
  - PD-L1 non-expressing (< 1% tumor cell membrane staining in a minimum of a hundred evaluable tumor cells)
- Histology
  - Squamous vs
  - Non-squamous

Subjects with tumors categorized as PD-L1 expressing (Part 1A) will be randomized and treated with one of the following open-label treatments:

- **Arm A**: Nivolumab 240 mg administered IV over 30 minutes every 2 weeks until disease progression or unacceptable toxicity. Nivolumab treatment beyond initial investigator-assessed RECIST 1.1 defined progression is permitted if the subject has investigator assessed clinical benefit and is tolerating nivolumab, as specified in Section 4.5.7.
- **Arm B**: 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 beyond initial investigator-assessed RECIST 1.1 defined progression is permitted if the subject has investigator assessed clinical benefit and is tolerating nivolumab, as specified in Section 4.5.7
- Arm C: Platinum-doublet chemotherapy administered in 3-week cycles for up to a maximum of 4 cycles of IV chemotherapy. Chemotherapy treatment will continue until disease progression, unacceptable toxicity or

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completion of the 4 cycles, whichever comes first. Choice of chemotherapy regimens is dependent on NSCLC histology.
- Squamous cell:
  - Gemcitabine (1000 or 1250 mg/ m^2) with cisplatin (75 mg/m^2). Gemcitabine administered on Day 1 and Day 8 of each cycle; or
  - Gemcitabine (1000 mg/ m^2) with carboplatin (AUC 5). Gemcitabine administered Day 1 and Day 8 of each cycle
- Non-squamous cell:
  - Pemetrexed (500 mg/m^2) with cisplatin (75 mg/m^2) administered on Day 1 of each cycle, or
  - Pemetrexed (500 mg/m^2) carboplatin (AUC 5 or 6) administered on Day 1 of each cycle

Subjects with tumors categorized as PD-L1 non-expressing (Part 1B) will be randomized and treated with one of the following open-label treatments:

- **Arm D**: 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 beyond initial investigator-assessed RECIST 1.1 defined progression is permitted if the subject has investigator assessed clinical benefit and is tolerating nivolumab, as specified in Section 4.5.7
- **Arm F**: Platinum-doublet chemotherapy administered in 3-week cycles for up to a maximum of 4 cycles of IV chemotherapy. Chemotherapy treatment will continue until disease progression, unacceptable toxicity or completion of the 4 cycles, whichever comes first. Choice of chemotherapy regimens is dependent on NSCLC histology.
  - Squamous cell:
    - Gemcitabine (1000 or 1250 mg/m^2) with cisplatin (75 mg/m^2). Gemcitabine is administered on Day 1 and Day 8 of each cycle; or
    - Gemcitabine (1000 mg/m^2) with carboplatin (AUC 5). Gemcitabine is administered on Day 1 and Day 8 of each cycle
  - Non-squamous cell:
    - Pemetrexed (500 mg/m^2) with cisplatin (75 mg/m^2) administered on Day 1 of each cycle; or
    - Pemetrexed (500 mg/m2) with carboplatin (AUC 5 or 6) administered on Day 1 of each cycle
- **Arm G:** Nivolumab administered IV over 30 minutes at 360 mg combined with platinum doublet chemotherapy administered IV up to maximum of 4 doses, followed by nivolumab administered IV over 30 minutes at 360 mg every 3 weeks until disease progression or unacceptable toxicity. Nivolumab treatment beyond initial investigator assessed RECIST 1.1 defined progression is permitted if the subject has investigator assessed clinical benefit and is tolerating nivolumab, as specified in Section 4.5.9

Enrollment of Part 1 will end after approximately 1200 subjects with PD-L1 expressing tumors (Part 1A) have been randomized. At this time, approximately 540 subjects with non-expressing tumors (Part 1B) are expected to be randomized.

In Part 1, the co- primary objective will be measured by the primary endpoints of OS and PFS assessed by BICR.

The study design schematic is presented in Figure 3.1.2-1.

Part 2

Subjects will be randomized 1:1 into 2 arms and stratified by the PD-L1 expression level (< 1% versus ≥ 1%), histology (squamous vs non-squamous), and gender (male versus female).

Note: Subjects with tumor samples unevaluable for PD-L1 status will be stratified to <1% group.

Subjects will receive open-label treatment with one of the following:

Arm H: Nivolumab combined with platinum-doublet chemotherapy administered every 3 weeks. Combination treatment will continue until disease progression, unacceptable toxicity or completion of the 4 cycles, whichever

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comes first. Subjects with squamous and non-squamous histologies who have stable disease or response after cycle 4 will continue nivolumab 360 mg as maintenance therapy every 3 weeks until disease progression or unacceptable toxicity. Subjects with non-squamous histology who have stable disease or response after cycle 4 may continue pemetrexed maintenance therapy with nivolumab. Choice of platinum-doublet regimens is dependent on NSCLC histology:

- Squamous:
  - Nivolumab 360 mg administered IV over 30 minutes, followed by paclitaxel (200 mg/m^2) with carboplatin (AUC 6) administered on Day 1 of each cycle every 21 days
- Non-squamous:
  - Nivolumab 360 mg administered IV over 30 minutes, followed by pemetrexed (500 mg/m^2) with cisplatin (75 mg/m^2) administered on day 1 of each cycle, or
  - Nivolumab 360 mg administered IV over 30 minutes, followed by pemetrexed (500 mg/m^2) with carboplatin (AUC 5 or 6) administered on Day 1 of each cycle

Arm I: Platinum-doublet chemotherapy administered in 3-week cycles for up to a maximum of 4 cycles of IV chemotherapy. Chemotherapy treatment will continue until disease progression, unacceptable toxicity or completion of the 4 cycles, whichever comes first. Choice of chemotherapy regimens is dependent on NSCLC histology:

- Squamous:
  - Paclitaxel (200 mg/m^2) with carboplatin (AUC 6) administered on Day 1 of each cycle every 21 days
- Non-squamous:
  - Pemetrexed (500 mg/m^2) with cisplatin (75 mg/m^2) administered on Day 1 of each cycle; or
  - Pemetrexed (500 mg/m^2) with carboplatin (AUC 5 or 6) administered on Day 1 of each cycle

Enrollment will end after approximately 750 subjects have been randomized into Arms H and I. Assuming a 35% screening failure rate, it is estimated that approximately 1153 subjects will be enrolled in order to have approximately 750 subjects randomized.

The primary endpoint for Part 2 is Overall Survival.

The study design schematic is presented in Figure 3.1.2-2.

Note (for Parts 1 and 2): Subjects with non-squamous histology (arm C, F or G, H, or I) who have stable disease or response after cycle 4 are permitted to continue pemetrexed alone as maintenance therapy until disease progression or unacceptable toxicity. The investigator must indicate, at the time of randomization, whether or not a subject will be treated with pemetrexed continuation maintenance if eligible to do so.

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 progression or treatment discontinuation, whichever occurs later. Subjects receiving nivolumab or nivolumab plus ipilimumab beyond investigator-assessed progression must also continue tumor assessments until such treatment has been discontinued.

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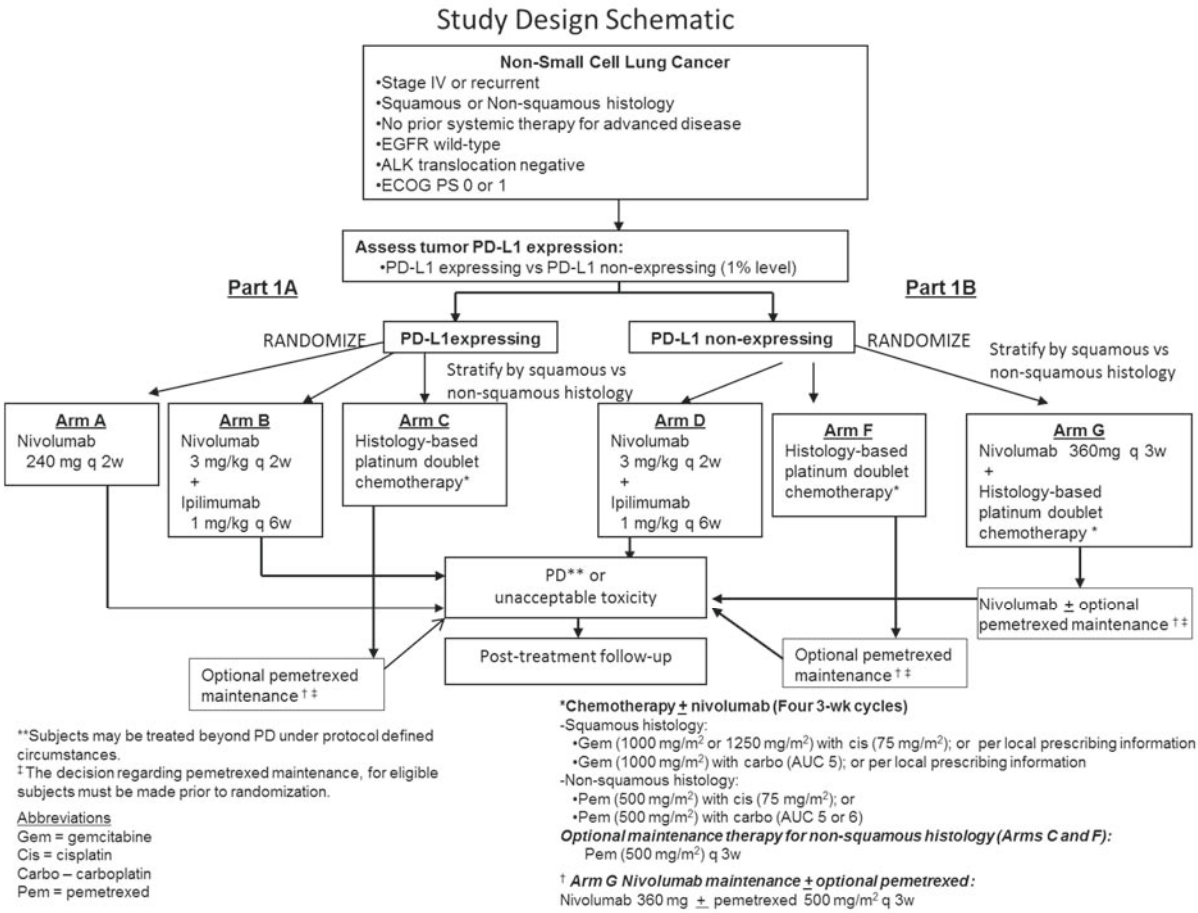

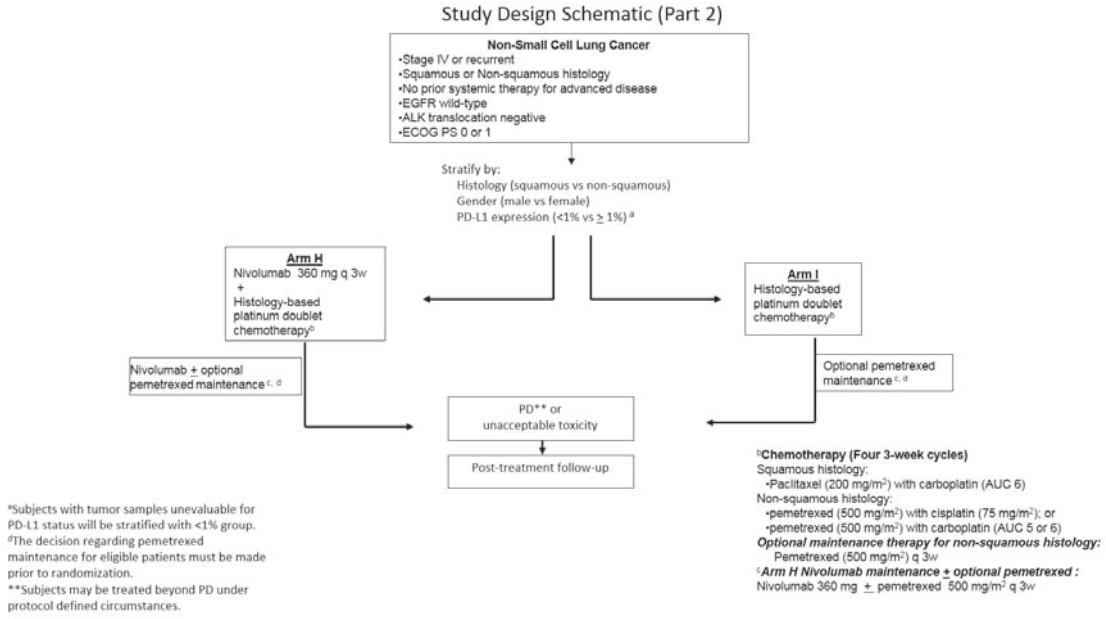

Study Population: Subjects must meet all eligibility criteria specified in Section 3.3 of the protocol, including the following:

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Key Inclusion Criteria

- ECOG Performance Status of ≤ 1
- Subjects with histologically confirmed Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer classification squamous or non-squamous histology, with no prior systemic anticancer therapy (including EGFR and ALK inhibitors) given as primary therapy for advanced or metastatic disease
- Measurable disease by CT or MRI per RECIST 1.1 criteria

Key Exclusion Criteria

- Subjects with known EGFR mutations which are sensitive to available targeted inhibitor therapy
- Subjects with known ALK translocations which are sensitive to available targeted inhibitor therapy
- Subjects with untreated CNS metastases are excluded, even if asymptomatic
- 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 randomization. Inhaled or topical steroids, and adrenal replacement steroid > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease

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

Study Drug for CA209227		
Medication	Potency	IP/Non-IP
Nivolumab	10 mg/ml	IP
Ipilimumab	5 mg/ml	IP
Carboplatin	10 mg/ml	IP
Cisplatin	1 mg/ml	IP
Gemcitabine	1000 mg/vial	IP
Pemetrexed	500 mg/vial	IP
Paclitaxel	100 mg/vial (6 mg/mL)	IP

Treatment with nivolumab or nivolumab with ipilimumab will be given for up to 24 months in the absence of disease progression or inacceptable toxicity. Chemotherapy will be given as per the study dosing schedule.

Study Assessments: Overall survival and PFS assessed by BICR are the co-primary endpoints of Part 1 and OS is the primary endpoint of Part 2. Overall survival is defined as the time from randomization to the date of death. Subjects will be assessed for response by CT or MRI beginning at 6 weeks (± 7 days) after first dose date and continuing every 6 weeks (± 7 days) until week 48 and then every 12 weeks (± 7 days) until progression or treatment discontinuation, whichever occurs later. Tumor assessments must continue per protocol until RECIST 1.1 progression is assessed by this Independent Review. A subject who has not died will be censored at last known alive date. 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. All randomized subjects will be evaluated.

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Statistical Considerations (Sample Size):

In Part 1 of the study, the overall enrolled population meeting the inclusion/exclusion criteria is categorized into PD-L1 expression level defined parts: PD-L1 expressing as Part 1A and PD-L1 non-expressing (<1%) as Part 1B. Subjects categorized within these pre-defined groups are then stratified by their histology status and randomized to the respective treatment arms in 1:1:1 ratio. The alpha (type-1 error) for assessing the co-primary and secondary efficacy objectives within Part 1 is set at a two sided 0.05 level.

In Part 2 of the study, subjects meeting the inclusion/exclusion criteria regardless of PD-L1 expression level are randomized after the conclusion of enrollment and randomization of Part 1. Subjects are stratified by histology status, PD-L1 expression level and gender and randomized to the respective treatment arms in 1:1 ratio. The sample size is prospectively specified and the alpha for assessing the primary and secondary efficacy objectives in Part 2 is set at a two sided 0.05 level independently from Part 1.

A total of 1740 subjects are planned to be randomized into Part 1A and Part 1B of this study, with approximately 1200 PD-L1 expressing subjects randomized at 1:1:1 ratio into the respective treatment arms (Arms A, B, and C) and approximately 540 PD-L1 non-expressing subjects randomized into the respective treatment arms (Arms D, F, and G). Assuming a 35% screening failure rate, it is estimated that approximately 2677 subjects will be enrolled in order to have 1740 subjects randomized.

A total of approximately 750 subjects are planned to be randomized into Part 2 of this study at 1:1 ratio to treatment arms (Arms H and I). Assuming a 35% screening failure rate, it is estimated that approximately 1153 subjects will be enrolled in order to have approximately 750 subjects randomized.

Sample size justification to support co-primary objective of OS comparison of arm B vs Arm C in Part 1A:

The sample size of Part 1A is calculated to compare OS between nivolumab in combination with ipilimumab (Arm B) and platinum doublet chemotherapy (Arm C) under a two-side 0.025 type I error with 90% power consideration for subjects with PD-L1 expressing ≥1%. The number of events was estimated assuming an exponential distribution for OS in each arm.

Approximately 1200 subjects will be randomized to the 3 treatment groups (Arms A, B and C) in a 1:1:1 ratio. Approximately 553 events (i.e., deaths), observed among approximately 800 subjects between Arm B and C provides 90% power to detect a hazard ratio (HR) of 0.74 with a type I error of 0.025 (two-sided). The HR of 0.74 corresponds to a 35% increase in the median OS, assuming a median OS of 13.8 months for platinum doublet chemotherapy (arm C) and 18.6 months for nivolumab in combination with ipilimumab (Arm B) respectively. One interim OS analyses is planned at 70% of total events observed at final analysis respectively. The stopping boundaries at the interim and final analyses will be based on the actual number of OS events at the time of the analysis using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. If the interim analyses are performed exactly at 387 events, the nominal significance level for OS superiority will be 0.006. The nominal significance level for the final look of OS after 553 events would then be 0.023.

Assuming a piecewise accrual rate (number of randomized subjects per month: 1 for the first four months, 27 for the next 3 months and followed by 120 subsequently) for PD-L1 expressing subjects, it will approximately take 40 months (18 months for accrual and 22 months for follow-up) from the randomization of the first subject to observe the required number of events among subjects randomized to Arm B and C for final OS analysis.

Table 8.1.1.1-1 summarizes the key parameters of the sample size justification in Part 1A of the study.

Table 8.1.1.1-1: Summary of Sample Size Parameters and Schedule of Analyses in Part 1A of the Study

Primary Endpoint	**OS**
Primary analysis population	PD-L1 expressing ≥ 1% in Arm B and Arm C
Power (interim analysis / final analysis)	90% (58% / 32%)

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Table 8.1.1.1-1: Summary of Sample Size Parameters and Schedule of Analyses in Part 1A of the Study

Primary Endpoint	**OS**
Alpha	0.025
Hypothesized Median OS (months): Chemotherapy(Arm C) vs. nivolumab + ipilimumab (Arm B)	13.8 vs. 18.6
Hypothesized Hazard ratio	0.74
Accrual Duration (months)	18
Timing of OS final analysis(from randomization of first subject (months)	40
Sample size (Arm B and Arm C)	800
Expected number of events for	
OS interim analysis (70% events)	387
OS final analysis	553

Sample size justification to support co-primary objective of PFS comparison of nivolumab + ipilimumab vs chemotherapy in subjects with baseline high TMB regardless of PD-L1 expression:

Approximately 221 PFS events observed among the high TMB subjects provides 80% power to detect a hazard ratio of 0.66 (nivolumab + ipilimumab vs. chemotherapy) with a two-sided type 1 error of 0.025. The HR of 0.66 corresponds to a 52% increase in the median PFS, assuming a median of 6 months for platinum doublet chemotherapy and 9.1 months for nivolumab in combination of ipilimumab. A HR of 0.66 is targeted based on observation from Checkmate 026, as well as based on what would be considered a clinically meaningful improvement in a biomarker selected population. No formal interim analysis of PFS is planned. To achieve 221 PFS events, a sample size of at least 265 subjects will be required.

Assuming a piecewise accrual rate with a18-month accrual period, it will take approximately 25 months from the randomization of the first subject to observed the required number of events for PFS analysis. The number of events needed for the analyses will be monitored by the un-blinded independent statistician supporting the DMC.

Table 8.1.1.2-1 summarizes the key parameters of the sample size justification in the part 1 of the study.

Table 8.1.1.2-1: Sample Size Justification in Part 1 of the Study

Primary Endpoint	**PFS**
Primary analysis Comparison population	Subjects with TMB high: nivolumab+ipilimumab (Pooled Arm B and Arm D) and chemotherapy (pooled Arm C and Arm F)
Power	80%
Alpha	0.025
Hypothesized Median PFS of chemotherapy (pooled Arm C and Arm F) vs. nivolumab+ipilimumab (pooled Arm B and Arm D)	6 vs. 9.1
Hypothesized Hazard ratio	0.66
Accrual Duration (months)	18

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Table 8.1.1.2-1: Sample Size Justification in Part 1 of the Study

Primary Endpoint	**PFS**
Timing of final analysis (FA) from randomization of first subject (months)	25
Estimated sample size	At least 265
Expected number of events for final analysis	221

Part 2

The sample size of part 2 of the study accounts for

- primary objective comparison of OS between: nivolumab in combination with chemotherapy (Arm H) and platinum doublet chemotherapy (Arm I) among subjects with non-squamous histology at randomization as stratified
- key secondary objective comparison of OS between: nivolumab in combination with chemotherapy (Arm H) and platinum doublet chemotherapy (Arm I),among all randomized subjects

Approximately 750 subjects will be randomized to the 2 treatment groups in a 1:1 ratio, stratified by the PD-L1 expression level (< 1% versus ≥ 1%), histology (squamous vs non-squamous), and gender (male versus female). It is expected that among them, approximately 540 subjects with non-squamous histology approximately 210 subjects with squamous histology will be randomized.

Sample size justification for OS comparison among non-squamous subjects

The sample size is calculated to compare OS between nivolumab in combination with chemotherapy (Arm H) and platinum doublet chemotherapy (Arm I), among subjects with non-squamous histology at randomization as stratified, under a two-side 0.05 type I error with 90% power consideration. The number of events was estimated assuming an exponential distribution for OS in each arm.

Approximately 311 events (ie, deaths), observed among the randomized non-squamous subjects, provides 90% power to detect a hazard ratio (HR) of 0.69 with an overall type 1 error of 0.05 (two sided). The HR of 0.69 corresponds to a 44.9% increase in the median OS, assuming a median OS of 13.3 months for platinum doublet chemotherapy (Arm I) and 19.3 months for experimental treatment arms (Arm H) respectively. It is projected that an observed hazard ratio of 0.796 or less, which corresponds to a 3.4 months or greater improvement in median OS (13.3 mo vs. 16.7 mo), would result in a statistically significant improvement in OS for the experimental arm at the final OS analysis.

One formal interim analysis of OS are is planned for this study, after observing approximately 230 events (74% of the targeted OS events for final analysis). The stopping boundaries at the interim and final analyses will be based on the actual number of OS events at the time of the analysis using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. If the interim analysis is performed exactly at 230 events and if the p-value is ≤ 0.018, then the OS among non-squamous subjects would be statistically significant per DMC. In the event that this interim analysis is not statistically significant, the nominal significance level for the final look of OS after 311events would then be 0.044 (adjusted for interim analysis).

Assuming a piecewise accrual rate and above stated OS distribution assumptions, it will approximately take 25 months from FPFV to observe the required number of OS events for the final OS analysis (9 months for accrual and 16 months for minimum follow up).

Table 1 summarizes the key parameters of the sample size justification for OS comparison among non-squamous subjects in the part 2 of the study.

Table -1: Sample Size Justification for Non-squamous Subjects in Part 2 of the Study

Primary Endpoint	**OS**
Primary analysis Comparison Population	Arm H and Arm I non-squamous subjects
Power (interim analysis/final analysis)	90% (67.5%/22.5%)
Alpha	0.05
Hypothesized Median PFS chemotherapy (arm I) vs. nivolumab + chemotherapy (arm H) (months)	13.3 vs 19.3
Hypothesized Hazard ratio	0.69
Accrual Duration (months)	9
Timing of final analysis(FA) from randomization of first subject (months)	25
Sample size for Arms H and I-non-squamous subjects	540
Expected number of events for	
OS interim analysis (74% events)	230
OS final analysis	311

Sample size justification for OS comparison among all randomized subjects

Comparison of OS among all randomized subjects is one of the key secondary objectives. Approximately 398 events (i.e., deaths), observed among all randomized subjects in part 2 provides 90% power to detect a hazard ratio (HR) of 0.72 with a type 1 error of 0.05 (two-sided). The HR of 0.72 corresponds to a 39% increase in the median OS, assuming a median OS of 13.3 months for platinum doublet chemotherapy (arm I) and 18.5 months for nivolumab in combination with chemotherapy (Arm H) respectively. One interim analysis of OS among all randomized subjects is planned at time of interim analysis of primary analysis of OS among non-squamous subjects. This formal interim comparison of OS among all randomized subjects would be conducted in a hierarchical manner, i.e. if the formal primary comparison of OS among non-squamous subjects is statistically significant then the formal comparison of OS among all randomized subjects would be conducted. The stopping boundaries at the interim and final analyses will be based on the actual number of OS events at the time of the analysis using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. If the interim analysis is performed exactly at 338 events, the study could be stopped by the DMC for OS superiority if the p-value is ≤ 0.03. In the event that this interim analysis is not statistically significant, the nominal significance level for the final look of OS after 398 events would then be 0.042 (adjusted for interim analysis). If the interim analysis for OS among non-squamous subjects is not positive, then the interim analysis of OS among all randomized subjects would not be conducted. The final analysis of OS among non-squamous subjects under such an instance would be conducted after observing 311 OS events in the non-squamous population. The final analysis for all randomized subjects would be conducted at the time of final analysis for non-squamous subjects.

Assuming a piecewise accrual rate, it will approximately take 25 months (9 months for accrual and 16 months for follow-up) from the randomization of the first subject to observe the required number of events among subjects randomized to Arm H and I for final OS analysis.

Table 8.1.3-1 summarizes the key parameters of the sample size justification in the part 2 of the study.

Table 8.1.3-1: Sample Size Justification in Part 2 of the Study

Primary Endpoint	**OS**
Primary analysis Comparison population	Arm H and Arm I
Power (interim analysis /final analysis	90% (80%/10%)

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Table 8.1.3-1: Sample Size Justification in Part 2 of the Study

Primary Endpoint	**OS**
Alpha	0.05
Hypothesized Median OS chemotherapy (arm I) vs. nivolumab + chemotherapy (arm H) (months)	13.3 vs 18.5
Hypothesized Hazard ratio	0.72
Accrual Duration (months)	7.5
Timing of final analysis(FA) from randomization of first subject (months)	22
Sample size (Arms H and I)	750
Expected number of events for	
OS interim analysis (85% events)	338
OS final analysis	398

Primary Endpoints:

In Part 1, the co- primary objective will be measured by the primary endpoints of OS and PFS assessed by BICR. In Part 2 the primary endpoint is OS.

OS is defined as the time between the date of randomization and the date of death due to any cause. OS will be censored on the last date a subject was known to be alive. OS will be followed continuously while subjects are on the study drug and every 3 months via in-person or phone contact after subjects discontinue the study drug.

PFS is defined as the time between the date of randomization and the first date of documented progression, as determined by BICR, or death due to any cause, whichever occurs first. Subjects who die without a reported progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subject who did not have any on study tumor assessments and did not die will be censored on their date of randomization. Subjects who had palliative local therapy or initiated anti-cancer therapy without a prior reported progression will be censored on the date of their last evaluable tumor assessment prior to or on the initiation of subsequent anti-cancer therapy or palliative local therapy. Tumor assessments are scheduled to be performed at week 6 (± 7 days) from first dose date, every 6 weeks until week 48 (± 7 days) and then every 12 weeks (± 7 days) until disease progression or treatment discontinuation, whichever occurs later.

Secondary Endpoints:

OS and PFS are also used to evaluate secondary objectives in Part 1 and Part 2. ORR is considered as a secondary endpoint in all individual substudies. ORR is defined as the number of subjects with a BOR of CR or PR divided by the number of randomized subjects for each treatment group. BOR is defined as the best response designation, recorded between the date of randomization and the date of objectively documented progression per RECIST 1.1 as determined by BICR or the date of initiation of palliative local therapy or the date of subsequent anti-cancer 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 study medication beyond progression, the BOR should be determined based on response designations recorded at the time of the initial RECIST 1.1 defined progression.

Time to response and duration of response are secondary endpoints for all individual substudies to support ORR endpoint.

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

Duration of objective response (DOR) is defined as the time between the date of first confirmed response to the date of the first documented tumor progression (per RECIST 1.1) per BICR assessment, or death due to any cause, whichever occurs first. Subjects who neither progress nor die will be censored on the date of their last evaluable tumor assessment. Subjects who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last evaluable tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy. DOR will be evaluated for responders (i.e. subjects with confirmed CR or PR) only as assessed by BICR.

Exploratory endpoints

Safety and tolerability objectives will be measured by the incidence of adverse events, serious events, deaths, and laboratory abnormalities.
Adverse event assessment and laboratory tests are performed at baseline, and continuously throughout the study at the beginning of each subsequent cycle.
Disease-Related Symptom Deterioration Rate by week 12 is defined as the proportion of subjects who had 10 points or more increase from baseline in the LCSS Average Symptom Burden Index (ABSI) score at any time between baseline and Week 12. The time to deterioration in symptoms, is defined by the time to a clinically meaningful change (10 points or more) from baseline in the LCSS average symptom burden index (ASBI). A formal definition will be discussed in the statistical analysis plan.
The LCSS is a measure of disease-related symptoms and quality of life suited to use in patients suffering from lung cancer. It includes six items measuring loss of appetite, fatigue, coughing, shortness of breath, hemoptysis, and pain. Three additional items measure overall symptom burden, disease-related functional limitations, and quality of life. The questionnaire uses a 24 hour recall period, and responses for each item are captured using a 100-mm visual analog scale (VAS). Scores for individual items ranging from 0 (no symptomatology or highest quality of life) to 100 (worst symptomatology or quality of life) are derived by dividing the length of the line drawn from the lowest possible response to the patient's response by the length of the VAS and multiplying the resulting quotient by 100. An average symptom burden index (ASBI) score can be derived as the average of scores for the six symptom-related items with a clinically meaningful change in ASBI score being defined as 10 points. Accordingly, a meaningful deterioration in symptoms as measured by the ASBI is reflected in a mean post-baseline score change 10 points.
PFS after next line of treatment (PFS-2) is defined as the time from randomization to the date of investigator-defined documented second objective disease progression after second-line therapy or death due to any cause, whichever comes first. Clinical deterioration will not be considered as progression. A subject who neither progresses nor dies will be censored on the date of his/her last adequate tumor assessment or last follow-up for progression/subsequent therapy. A subject who does not have any post-baseline tumor assessments and who has not died will be censored on the date at which he/she was randomized.
The PK objective will be measured from serum concentration. Samples will be collected to characterize pharmacokinetics of nivolumab and to explore exposure-safety and exposure - efficacy relationships.

Statistical Analyses:

Statistical analyses outlined in this section are applicable across endpoints and populations in general, unless otherwise specified. Analyses for primary endpoint will be performed at scheduled interim and final analyses. If the pre-specified OS superiority boundaries are crossed at the scheduled interim analyses and the corresponding sub study or substudies are unblinded, the secondary and exploratory endpoints will also be analyzed. Potential integrated analysis may be performed cross substudies depending on the availability of data at the time of analysis. Additional details will be provided in statistical analysis plan.

Primary Endpoint Methods:

Progression free survival in TMB high subjects in Part 1:

PFS per BICR assessment co-primary hypothesis testing for nivolumab in combination with ipilimumab (pooled Arms B and D) to platinum-doublet chemotherapy (pooled Arms C and Arm F) in subjects with high baseline TMB

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regardless of PD-L1 expression level will be based on a unstratified log-rank test using a two-sided alpha 0.025. No PFS interim analysis is planned for this analysis population.

Hazard ratios (HR) of PFS (nivolumab in combination of ipilimumab vs. platinum doublet chemotherapy) and corresponding two-sided 97.5 % confidence intervals (CI) will be estimated using an unstratified Cox proportional hazard model, with treatment group as a single covariate.

PFS curves, PFS medians with 95% CIs, and PFS rates at 6, 12, 18, and 24 months with 95% CIs will be estimated by treatment group using Kaplan-Meier methodology.

Overall Survival in Part 1A:

There are two scheduled OS analyses each for Part 1A: one OS interim analysis (IA) and one OS final analysis (FA).

1) OS co-primary hypothesis testing for nivolumab in combination of ipilimumab (Arm B) and platinum doublet chemotherapy (Arm C) with baseline PD-L1 expression ≥ 1% will be based on a two-sided stratified log-rank test stratified by histology.

The alpha spending allocated to the testing is based on the number of events at the time of interim analyses based on Lan-DeMets alpha spending function.

Hazard ratios (HR) of OS (Arm B vs. Arm C, Arm A vs. Arm C or Arm B vs. Arm A) and corresponding two-sided confidence intervals (CI) will be estimated using a stratified Cox proportional hazard model, with treatment group as a single covariate.

OS curves, OS medians with 95% CIs, and OS rates at 6, 12, 18, 24, 36, and 48 months with 95% CIs will be estimated by treatment group using Kaplan-Meier methodology if follow-up requirement is met.

Overall survival in Part 2:

There are two scheduled OS analyses for non-squamous subjects in Part 2: one OS interim analysis and one OS final analysis. OS primary hypothesis testing for nivolumab in combination with chemotherapy (Arm H) and chemotherapy (Arm I), among non-squamous subjects will be based on a two-sided stratified log-rank test stratified by PD-L1 expression and gender. The alpha spending allocated to the testing is based on the number of events at the time of interim analyses based on Lan-DeMets alpha spending function.

Hazard ratios of OS (Arm H vs. Arm I) and corresponding two-sided 95% confidence intervals will be estimated using a Cox proportional hazard model, with treatment group as a single covariate stratified by PD-L1 expression and gender. OS curves, OS medians with 95% CIs, and OS rates at 6, 12, 18, 24, 36, and 48 months with 95% CIs will be estimated by treatment group using Kaplan-Meier methodology if follow-up requirement is met. Similar analysis would be conducted for comparison of OS among all randomized subjects, towards the secondary objective in Part 2.

Secondary Endpoint Methods:

Hierarchical Testing Procedure:

Hierarchical Testing Procedure (Part 1 TMB co-primary objective paradigm)

If the superiority of PFS per BICR assessment for the comparison between nivolumab in combination with ipilimumab (pooled Arms B and D) and platinum-doublet chemotherapy (pooled Arms C and F) among high baseline TMB subjects is demonstrated at a two sided type I error rate 0.025, a hierarchical hypothesis testing approach for the secondary endpoints will be used at the following order:

1) PFS per BICR assessment of nivolumab (Arm A) to platinum-doublet chemotherapy (Arm C) in subjects whose tumors have ≥ 1% PD-L1 expression and with baseline high tumor mutation burden. This comparison is based on a two-sided unstratified log-rank test.

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2) OS of nivolumab in combination with ipilimumab (Arms B and D) to platinum-doublet chemotherapy (Arms C and F) in subjects with high baseline tumor mutation burden regardless PD-L1 expression level. This comparison is based on a two-sided unstratified log-rank test. This test will be performed if OS data are mature and Part 1A OS data are unblinded.

3) OS of nivolumab (Arm A) to platinum-doublet chemotherapy (Arm C) in subjects whose tumors have ≥ 1% PD-L1 expression and with high baseline tumor mutation burden. This comparison is based on a two-sided unstratified log-rank test. This test will be performed if OS data are mature and Part 1A OS data are unblinded.

The methodology used to analyze PFS and OS for the primary endpoint will also be used to analyze the secondary objectives in Part 1.

Hierarchical Testing Procedure (Part 1A OS co-primary objective paradigm)

If the superiority of OS is demonstrated for subjects in nivolumab in combination of ipilimumab (Arm B) and platinum doublet chemotherapy (Arm C) with baseline PD-L1 expression ≥ 1% at either interim analysis or final analysis, a hierarchical hypothesis testing approach for the secondary endpoints will be used at the following order to preserve the type I error rate at 0.025 in Part 1A. All the comparison will be performed under the same alpha level as used in the primary OS comparison.

1) PFS, based on BICR assessment, of nivolumab in combination with platinum-doublet chemotherapy (Arm G), to platinum-doublet chemotherapy (Arm F) in subjects whose tumors do not express PD-L1 (<1%)
2) OS of nivolumab in combination with platinum-doublet chemotherapy (Arm G) to platinum-doublet chemotherapy (Arm F) in subjects whose tumors do not express PD-L1 (<1%).
3) OS of nivolumab monotherapy (Arm A) to platinum-doublet chemotherapy (Arm C) in subjects whose tumors have ≥ 50% PD-L1 expression

Hierarchical testing procedure (Part 2 OS objective paradigm):

An overall hierarchical testing procedure will be used to assess the secondary objective of comparing OS among all randomized subjects, if the primary comparison of OS among non-squamous subjects is statistically significant.

A separate group sequential spending function will be used to adjust for the overall Type I error at the interim and final analysis for each of the two formal comparisons of OS objectives (among non-squamous subjects and among all randomized subjects). The actual level of significance at which each objective is assessed will be determined based on the individual group sequential spending function and the amount of information spent at the time of the analysis. If the interim analysis for OS among non-squamous subjects is not positive, then the interim analysis of OS among all randomized subjects would not be conducted. The final analysis of OS among non-squamous subjects under such an instance would be conducted after observing 311 OS events in the non-squamous population. The final analysis for all randomized subjects would be conducted at the time of the final analysis for non-squamous subjects. This procedure will ensure that the overall experiment-wise Type I error rate for the study is controlled at the 0.05 level.

The following are also secondary objectives but not part of the hierarchy:

In subjects with non-squamous histology:

- To compare the OS of nivolumab in combination with platinum-doublet chemotherapy (Arm H, among high baseline tumor mutation burden (≥ 10 mut/Mb subgroup
- To compare the PFS, based on BICR assessment, of nivolumab in combination with platinum-doublet chemotherapy (Arm H), to platinum-doublet chemotherapy (Arm I)
- To compare the ORR (BICR assessment) of nivolumab in combination with platinum doublet chemotherapy (Arm H), to platinum-doublet chemotherapy (Arm I)

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- To evaluate efficacy (OS, PFS, and ORR) by PD-L1 expressing levels for nivolumab in combination with platinum-doublet chemotherapy (Arm H) and platinum-doublet chemotherapy (Arm I)
- To evaluate efficacy (OS, PFS, and ORR) by TMB levels for nivolumab in combination with platinum-doublet chemotherapy (Arm H) and platinum-doublet chemotherapy (Arm I)

In all randomized subjects (ITT population):

- In subjects with high baseline tumor mutation burden (≥ 10 mut/Mb): To compare the OS of nivolumab in combination with platinum-doublet chemotherapy (Arm H)
- To compare the PFS, based on BICR assessment, of nivolumab in combination with platinum-doublet chemotherapy (Arm H), to platinum-doublet chemotherapy (Arm I)
- To compare the ORR (BICR assessment) of nivolumab in combination with platinum-doublet chemotherapy (Arm H), to platinum-doublet chemotherapy (Arm I)
- To evaluate efficacy (OS, PFS, and ORR) by PD-L1 expressing levels for nivolumab in combination with platinum-doublet chemotherapy (Arm H) and platinum-doublet chemotherapy (Arm I)
- To evaluate efficacy (OS, PFS, and ORR) by TMB levels for nivolumab in combination with platinum-doublet chemotherapy (Arm H) and platinum-doublet chemotherapy (Arm I)

Methods for OS and PFS as a secondary endpoint in Part 1and Part 2:

For Part 1 methodology used to analyze OS and PFS as secondary endpoints will be very similar as that used to analyze OS and PFS as primary endpoint except the hierarchical testing procedure consideration.

For Part 2, PFS comparison of nivolumab in combination with chemotherapy (Arm H) with platinum-doublet chemotherapy (Arm I) will be conducted, stratified by histology, PD-L1 expression and gender.

Hazard ratios of PFS (Arm H vs. Arm I) and corresponding two-sided 95% confidence intervals will be estimated using a Cox proportional hazard model, with treatment group as a single covariate, stratified by histology. PD-L1 expression and gender, PFS curves, PFS medians with 95% CIs, and PFS rates at 6, 12, 18, 24, 36, and 48 months with 95% CIs will be estimated using Kaplan-Meier methodology if follow-up requirement is met.

Methods for ORR, time to response and duration of response:

ORR in TMB high subjects of Part 1:

BICR-determined ORR among high TMB subjects (for nivolumab in combination of ipilimumab related analysis and for nivolumab monotherapy related analysis) in Part 1 will be estimated and its corresponding 95% exact two-sided CIs will be calculated using the Clopper Pearson method. The unweighted differences in ORR between the two treatment groups and corresponding 95% two-sided CI using the method of Newcombe will be provided. BOR as determined by BICR will be summarized by response category for each treatment group.

ORR in Part 2:

BICR-determined ORR in Part 2 will be estimated and its corresponding 95% exact two-sided CIs will be calculated using the Clopper Pearson method. The unweighted differences in ORR between the two treatment groups and corresponding 95% two-sided CI using the method of Newcombe will be provided. BOR as determined by BICR will be summarized by response category for each treatment group.

Time To Response and Duration Of Response in Part 1 and Part 2:

Time to response and duration of response are secondary/exploratory endpoints in all substudies (Part 1A, Part 1B and Part 2). Summary statistics of time to objective response will be provided for each treatment group for subjects who achieve PR or CR for individual sub study separately.

Duration of response in each treatment group will be estimated using KM product-limit method for subjects who achieve PR or CR for individual sub study separately. Median values along with two-sided 95% CI will be calculated. Summary statistics will be computed constructed based on a log-log transformed CI for the survivor function. Additional sensitivity analysis for DOR will be specified in the SAP.

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Exploratory Analyses

PFS-2 is defined as the time from randomization to the date of investigator-defined documented second objective disease progression after second-line therapy or death due to any cause, whichever comes first. Clinical deterioration will not be considered as progression. A subject who neither progresses nor dies will be censored on the date of his/her last adequate tumor assessment or last follow-up for progression/subsequent therapy. A subject who does not have any post-baseline tumor assessments and who has not died will be censored on the date at which he/she was randomized.

Outcome Research Analysis

Outcome research analysis will be performed for the target populations of interest at the time of final analysis of OS or PFS. Both the LCSS and EQ 5D questionnaire completion rates, defined as the proportion of questionnaires actually received out of the expected number (i.e., the number of subjects still on treatment in follow-up), will be calculated and summarized at each assessment point.

The disease-related symptom deterioration rate by week 12 and the corresponding 95% exact CI will also be calculation by Clopper-Pearson method for the target population of interest in each treatment group. The time to deterioration in symptoms, as defined by the changes from baseline in the LCSS average symptom burden index (ASBI) will be calculated using Kaplan-Meier methods. The LCSS ASBI score and the within-patient change from baseline at each LCSS assessment point will be summarized using descriptive statistics (N, mean, median, SD, 25th and 75th percentiles, 95% CI) for the target population of interest in each treatment group. Similarly, both the EQ-5D utility index and the EQ-5D visual analogue scale (EQ-5D VAS) and their respective within-patient changes from baseline at each assessment point will be summarized using descriptive statistics (N, mean, median, SD, 25th and 75th percentiles, 95% CI) for the target population of interest in each treatment group. In addition, the proportion of subjects reporting each of the 3 problems levels (no problems, some problems, extreme problems) for the 5 EQ-5D dimensions at each assessment time point will be summarized by level of problem and for the target population of interest in each treatment group. Percentages will be based on number of subjects responding at each assessment time point.

Safety analysis

Safety analysis will be performed in all treated subjects for each sub study. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 by treatment group. All on-study AEs, drug-related AEs, SAEs and drug-related SAEs will be tabulated using worst grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term. On-study lab parameters including hematology, chemistry, liver function and renal function will be summarized using worst grade per NCI CTCAE v 4.0 criteria.

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1 INTRODUCTION AND STUDY RATIONALE

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related mortality worldwide, accounting for approximately 18% of all cancer deaths.[1] Despite treatment with platinum-based chemotherapy, the standard of care for first-line therapy patients with metastatic NSCLC have a median survival of approximately 10 months, and a 5-year survival rate of less than 5%.[2]

Immunotherapeutic approaches recently have demonstrated clinical efficacy in several cancer types, including melanoma and hormone-refractory prostate cancer.[3] Tumors may modulate and evade the host immune response through a number of mechanisms, including down regulation of tumor-specific antigen expression and presentation, secretion of anti-inflammatory cytokines, and upregulation of inhibitory ligands. T cell checkpoint regulators such as CTLA-4 and programmed death-1 (PD-1, CD279) are cell surface molecules that, when engaged by their cognate ligands, induce signaling cascades down-regulating T cell activation and proliferation. One proposed model by which therapeutic T cell checkpoint inhibitors derive antitumor activity is through breaking of immune tolerance to tumor cell antigens.

Nivolumab (BMS-936558) is a fully human, IgG4 (kappa) isotype mAb that binds PD-1 on activated immune cells and disrupts engagement of the receptor with its ligands PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273), thereby abrogating inhibitory signals and augmenting the host antitumor response. In early clinical trials, nivolumab has demonstrated activity in several tumor types, including melanoma, renal cell cancer (RCC), and NSCLC.[4]

Nivolumab is now approved in the U.S. and in Europe to treat metastatic non-small cell lung cancer in patients with progression on or after platinum-based chemotherapy. The approval was based on the results of CA209017, CA209063, and CA209057. In CA209017, a randomized trial of nivolumab versus docetaxel in previously treated squamous NSCLC, the median overall survival (OS) for subjects in the nivolumab arm was 9.2 months versus 6 months for those in the docetaxel arm (HR = 0.59). Improvement in survival was observed for nivolumab regardless of PD-L1 expression, though there was a trend for better efficacy for those with PD-L1 expressing tumors.[5] A single arm trial (CA209063) of 117 subjects with metastatic squamous cell NSCLC, with progression after platinum-based chemotherapy and at least one additional systemic regimen, showed a 15% overall response rate (ORR), of whom 59% had response durations of 6 months or longer.[6]

A second phase 3 study, CA209057, was also stopped at a preplanned interim analysis by the independent Data Monitoring Committee (DMC), meeting its primary endpoint of superior overall survival of nivolumab versus docetaxel in subjects with previously-treated non-squamous NSCLC.[7] Subjects in the nivolumab arm had a 27% reduction in risk of death (HR = 0.73; P = 0.0015). Interaction p-values, reported for PD-L1 expression subgroups by each of the pre-defined expression levels, suggested a clinically important signal of a predictive association. Nivolumab also significantly improved ORR vs docetaxel (P=0.0246), with ORR as high as 36% in subjects with PD-L1 expressing tumors. OS approximately doubled with nivolumab vs

docetaxel across the PD-L1 expression continuum. In contrast, no difference in OS was seen between nivolumab and docetaxel when PD-L1 was not expressed in the tumor.

In previously untreated, advanced or metastatic NSCLC (stage IV or recurrent) with ≥ 5% or ≥ 1% tumor PD-L1 expression, nivolumab did not show superior progression free survival (PFS) versus standard platinum doublet chemotherapy (Checkmate 026, HR 1.15 and 1.17 in subjects with ≥ 5% and ≥ 1% tumor PD-L1 expression respectively).[8] However, while not superior to chemotherapy, nivolumab clearly demonstrated activity, with an ORR of 26.1% in subjects with ≥ 5% tumor PD-L1 expression (24% in subjects with ≥ 1% tumor PD-L1 expression), and similar overall survival compared to chemotherapy with a HR 1.02 in subjects with ≥ 5% tumor PD-L1 expression (HR = 1.07 in subjects with ≥ 1% tumor PD-L1 expression).

In general, nivolumab also has been well tolerated to date, with a favorable safety profile relative to anticipated toxicities based on an immunostimulatory mechanism of action.[9]

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

In a phase 1 study (CA209004) of the combination of nivolumab plus ipilimumab in advanced melanoma, there was a 41% response rate, including a 17% complete response rate (CR).[10] A randomized phase 2 study (CA209069) comparing nivolumab plus ipilimumab versus ipilimumab showed an objective response rate of 61%, including a 22% complete response rate, in previously untreated, advanced melanoma subjects with BRAF wild-type mutation status, versus 11 % for ipilimumab alone.[11] In addition, the combination regimen decreased the risk of melanoma progression or death compared to ipilimumab alone by 60%. Similar results were also observed in BRAF mutation-positive subjects.

In a phase 1 (CA209012) study in subjects with NSCLC, the combination of nivolumab plus ipilimumab combination was evaluated at several different doses and schedules (Section 1.1.1). While the schedule evaluated in melanoma was not found to be tolerable in NSCLC, the study identified alternative schedules with an acceptable tolerability profile and encouraging activity, with response rates nearly twice the response rate observed with nivolumab monotherapy, thus providing an opportunity for superior outcomes with this combination compared to platinum doublet in a broad patient population. In the same study, nivolumab was also evaluated in combination with first-line platinum doublet chemotherapy.

Higher PD-L1 expression is associated with increased magnitude of benefit from PD-1 and PD-L1 inhibitors.[12], [13] However, durable responses are also observed in PD-L1 low or negative tumors, suggesting that additional biomarkers are needed to better identify patients who will benefit from immunotherapy.

Recently, emerging evidence across multiple tumor types suggests tumor mutational burden (TMB) is associated with increased benefit from PD-1, PD-L1 and CTLA-4 inhibition.[14, 15, 16] In Checkmate 026, subjects in the tertile with the highest tumor mutational burden derived a PFS benefit from nivolumab versus chemotherapy (HR...HR = 0.62; 95% CI: 0.38, 1.00); in contrast, in the subjects with medium and low tumor mutational burden (lower two tertiles), benefit from chemotherapy appears to be greater than with nivolumab. Importantly, TMB appears to be independent from PD-L1 expression, both in its distribution as well as its predictivity for benefit from immunotherapy.[16]

CA209227 (CheckMate 227, CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 227) is a randomized, open-label Phase 3 trial of nivolumab monotherapy or nivolumab plus ipilimumab or nivolumab plus platinum doublet chemotherapy versus platinum doublet chemotherapy alone in subjects with chemotherapy naive stage IV or recurrent NSCLC. The central questions of the study will be to determine if:

Part 1: in chemotherapy-naïve subjects with stage IV or recurrent PD-L1 expressing NSCLC, nivolumab plus ipilimumab improves overall survival (OS) compared with platinum doublet chemotherapy, and in chemotherapy-naïve subjects with stage IV or recurrent NSCLC with high tumor mutation burden (TMB) high at baseline regardless of PD-L1 status, nivolumab in combination with ipilimumab, will improve PFS compared with platinum-doublet chemotherapy.

Part 2: nivolumab plus platinum doublet chemotherapy, improves OS compared with platinum doublet chemotherapy in subjects with stage IV or recurrent NSCLC, regardless of PD-L1 expression level.

Organizing the study into distinct parts allows for the ability to address several important questions within a single study. Of note, the eligibility criteria are the same for Parts 1 and 2, allowing for easier comparison of different treatment options, as well as potential of pooling of results across different parts of the study. In Part 1, the randomization schemes are based on the PD-L1 expression of the subjects' tumor, thus allowing subjects with PD-L1 expressing and non-expressing tumors to participate. Given concurrent enrolment and randomization of all arms in part 1, at the same sites with no capping of any of the cohorts, allows for pooling of subjects across arms with the same treatments in part 1. Part 2 is open to all subjects including those with PD-L1 expressing and non-expressing tumors, as well as those whose PD-L1 expression cannot be determined. Part 2 may also be considered as an expansion of Part 1B to further evaluate the effect of adding nivolumab to chemotherapy in subjects with PD-L1 expressing tumors, as well as those with PD-L1 non-expressing tumors.

1.1 Study Rationale

1.1.1 Rationale for Dose Selection and Schedule of Nivolumab in Combination with Ipilimumab (Part 1, Arms B and D)

Preclinical data indicate that the combination of PD-1 and CTLA-4 receptor blockade may improve antitumor activity. In vitro combinations of nivolumab plus ipilimumab increase IFN-γ production 2- to 7-fold over either agent alone in a mixed lymphocyte reaction. Increased

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antitumor activity of the combination was also observed in 3 of 5 syngeneic murine cancer models. In a murine melanoma vaccine model, blockade with either CTLA-4 or PD-1 antibodies increased the proportion of CTLA-4 and PD-1-expressing CD4/CD8 tumor infiltrating T effector cells, and dual blockade increased tumor infiltration of T effector cells and decreased intratumoral T regulatory cells, as compared to either agent alone.[17]

The combination of nivolumab and ipilimumab was evaluated in CA209004 (MDX1106-04), a Phase 1b multiple ascending dose study in subjects with treatment-naive and previously treated advanced melanoma. Results showed promising activity with higher, but tolerable toxicity than ipilimumab alone.[18] Based on these data, CA209069, a phase 2 study, compared the combination to ipilimumab alone in treatment-naïve patients with advanced melanoma: nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks x4 followed by nivolumab 3 mg/kg every 2 weeks versus ipilimumab 3 mg/kg every 3 weeks x 4.[10] In patients with BRAF wild type tumors, the ORR was 61% (44/72), including 22% (16/72) complete responses (CR) in the group treated with the combination, compared to 11% (4/37) with 0 CRs in those treated with ipilimumab alone. The median PFS was not reached in the combination versus 4.4 months for ipilimumab alone (HR=0.4). It should be noted that in the combination group, the ORR was independent of PD-L1 expression. In this group, ORR was 58% among patients with PD-L1 expressing tumors and 55% among those with PD-L1 non- expressing tumors. In contrast, in the ipilimumab alone group, the ORR was numerically higher among patients with PD-L1 expressing tumors (18%) compared to those with PD-L1 non- expressing tumors (4%). Grade 3-4 treatment-related AEs were reported in 54% of patients receiving the combination compared to 24% for ipilimumab alone.

Ipilimumab has been shown to have activity in lung cancer.[19] However, the addition of ipilimumab to standard chemotherapy, without additional PD-1 inhibition, did not prolong overall survival in two phase 3 studies in NSCLC and SCLC respectively.

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

- nivolumab 1 mg/kg + ipilimumab 3 mg/kg, q 3 weeks x4, followed by nivolumab 3 mg/kg q 2 weeks (arms G and H, n=24);
- nivolumab 3 mg/kg + ipilimumab 1 mg/kg, q 3 weeks x4, followed by nivolumab 3 mg/kg q 2 weeks (arms I and J, n=25)

These regimens resulted in significant toxicity, with 39% of patients discontinuing treatment due to a treatment-related adverse event.
Thus, additional combination cohorts were initiated (arms N, O, P, Q), using lower doses of both nivolumab and ipilimumab, or the approved dose of nivolumab with frequent dosing of ipilimumab. These new regimens were much better tolerated, and the safety data are not dissimilar to what has been observed in the nivolumab monotherapy cohort (arm F in CA209012). (See Table 1.1.1-1).

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Table 1.1.1-1: Treatment-related adverse events from selected cohorts in CA209012

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

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

[b] based on August 2015 database lock.

[c] based on March 2015 database lock

Activity was observed in all cohorts, with response rates greater than 30% in the 2 cohorts in which nivolumab was dosed at 3 mg/kg (N3). Follow-up time is limited, but PFS and OS are also encouraging in the N3 cohorts (Table 1.1.1-2).

Table 1.1.1-2: Efficacy of First-Line Treatment of Nivolumab/Ipilimumab Combination

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

Activity was evaluated by PD-L1 expression (Table 1.1.1-3 and Table 1.1.1-4). Clinical activity was observed in subjects with both PD-L1 expressing and non-expressing tumors, though there was a greater magnitude of efficacy in the expressers.

Table 1.1.1-3: Efficacy by Tumor PD-L1 Expression (≥ 1%)

	Nivo 1 + Ipi 1 Q3W (n=12)	Nivo 1 Q2W + Ipi 1 Q6W (n=21)	Nivo 3 Q2W + Ipi 1 Q12W (n=21)	Nivo 3 Q2W + Ipi 1 Q6W (n=23)
ORR, %	8	24	48	48
mPFS, wks (95% CI)	11.5 (7.1,)	21.1 (11.4,)	34.6 (15.9, 35.3)	NR (15.4,)
PFS rate at 24 wks, % (95% CI)	42 (15,67)	40 (18, 61)	74 (48,88)	65 (42, 81)

Table 1.1.1-4: Efficacy by Tumor PD-L1 Expression (<1%)

	Nivo 1 + Ipi 1 Q3W (n=13)	Nivo 1 Q2W + Ipi 1 Q6W (n=7)	Nivo 3 Q2W + Ipi 1 Q12W (n=9)	Nivo 3 Q2W + Ipi 1 Q6W (n=7)
ORR, %	15	14	22	0
mPFS, wks (95% CI)	34.0 (8.9,)	NR (10.1,)	23.1 (4.0,)	10.3 (7.4, 12.7)
PFS rate at 24 wks, % (95% CI)	57 (25, 80)	NC	39 (9, 69)	0

Again, activity was greater in the N3 cohorts compared to the 2 cohorts in which nivolumab was dosed at 1 mg/kg every 2 weeks (N1). In subjects with PD-L1 expressing tumors (≥ 1% level), the response rate was 48% with nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 6 or every 12 weeks. For subjects with PD-L1 non-expressing tumors, the response rates were lower, but the subject numbers are small. The numerically highest response rate was observed with one of the schedules evaluating the approved dose of nivolumab 3 mg/kg (ipilimumab every 12 weeks). In contrast, there were no responses in the other schedule using the 3 mg/kg dose, in which the ipilimumab was dosed more frequently (every 6 weeks). It would be expected that the ipilimumab every 6 week schedule would be more active in the absence of safety issues, which were not observed. However, these cohorts have small numbers of subjects, so it is difficult to draw any firm conclusions. So, for subjects with PD-L1 expressing and non-expressing tumors, the nivolumab + ipilimumab schedule which will be evaluated is:

Nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks, i.e., the approved dose of nivolumab in pretreated NSCLC and the highest dose and frequency of ipilimumab feasible.

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Nivolumab plus Ipilimumab in NSCLC: Updated Results from CA209012

The data from CA209012 have been updated, and a summary efficacy for subjects treated with nivolumab 3 mg/kg plus ipilimumab is provided in Table 1.1.1-5. The promising efficacy observed in the N3 cohorts was confirmed.

Table 1.1.1-5: Efficacy of First-Line Treatment of Nivolumab (3 mg/kg) plus Ipilimumab (1 mg/kg)

	Nivo 3 Q2W + Ipi 1 Q12W (n=38)	Nivo 3 Q2W+ Ipi 1 Q6W (n=39)
Confirmed ORR, % (95% CI)	47 (31, 64)	39 (23,55)
PFS rate at 12 months (95% CI)	48 (31, 63)	35 (20,50)
Median OS, months (95% CI)	NR (14.0,)	18.1 (13.3, 18.1)
1-year OS rate, % (95% CI)	NC	69 (53, 81)

Source: Database lock date: 1-Feb-2016

The safety of the combination was also confirmed, as shown in Table 1.1.1-6. There were no treatment-related deaths.

Table 1.1.1-6: Safety Summary of Nivolumab (3 mg/kg) plus Ipilimumab (1 mg/kg) in First-Line NSCLC

	Nivo 3 Q2W + Ipi 1 Q12W (n=38)		Nivo 3 Q2W+ Ipi 1 Q6W (n=39)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Treatment-related AEs	82	37	72	33
Treatment-related AEs leading to discontinuation, %	11	5	13	8

Source: Database lock 1-Feb-2016

1.1.2 Rationale for Nivolumab Monotherapy in Subjects with PD-L1 Expressing Tumors (Part 1A,Arm A)

Nivolumab significantly prolonged overall survival versus docetaxel in two phase 3 trials in subjects with squamous (CA209017) and non-squamous (CA209057) NSCLC progressing during or after a first-line platinum doublet. While nivolumab did not show superior progression-free survival versus platinum doublet as first-line therapy in subjects with ≥ 5% or ≥ 1% tumor PD-L1 expression (CA209026), survival was similar for nivolumab monotherapy and a platinum based doublet. The inclusion of nivolumab for subjects with PD-L1 expressing tumors will provide a possibility to 1) estimate the contribution of ipilimumab to nivolumab, 2) further evaluate nivolumab monotherapy in subgroups with different PD-L1 expression levels, some of which were

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not sufficiently powered in Checkmate 026, and 3) evaluate safety and efficacy of a 240 mg q2w flat dose of nivolumab.

CA209017 was an open-label study in which 272 previously treated patients with metastatic squamous NSCLC were randomized to either nivolumab (n=135) or docetaxel (n=137).[5] There was a statistically significant improvement in OS (median 9.2 months versus 6.0 months, Hazard Ratio [HR] = 0.59), PFS (median 3.5 months versus 2.8 months, HR = 0.62), and response rate (20% versus 9%) for patients in the nivolumab arm. The expression of the PD-1 ligand (PD-L1) was neither prognostic nor predictive of benefit. Treatment-related adverse events (AEs) of grade 3 or 4 were reported in 7% of the patients in the nivolumab group as compared with 55% of those in the docetaxel group.

CA209057 was an open-label study in which 582 previously treated patients with metastatic non-squamous NSCLC were randomized to either nivolumab (n=292) or docetaxel (n=290).[7] There was a statistically significant improvement in OS (median 12.2 months versus 9.4 months, HR = 0.73) and response rate (19% versus 12%) for patients in the nivolumab arm. Nivolumab was associated with longer OS and PFS than docetaxel at the prespecified PD-L1 expression levels of 1% or higher, 5% or higher, and 10% or higher. Treatment-related AEs of grade 3 or 4 were reported in 10% of the patients in the nivolumab group, as compared with 54% of those in the docetaxel group.

CA209026 was an open-label, phase 3 study that compared the efficacy and safety of nivolumab and investigator's choice of platinum-based doublet chemotherapy as first-line therapy in patients with stage IV or recurrent PD-L1–positive NSCLC.[8] The primary endpoint, PFS per Independent Radiology Review Committee (IRRC), was not met. In the population in which PD-L1 expression was ≥ 5%, the median PFS was 4.2 months in the nivolumab arm versus 5.9 months in the chemotherapy arm (HR = 1.15). However, the OS was similar in both arms (nivolumab 14.4 months versus chemotherapy 13.2 months, HR = 1.02), despite that 60.4% of subjects in the chemotherapy arm subsequently received nivolumab. Safety results were consistent with the known safety profile of nivolumab; there were fewer treatment-related grade 3–4 adverse events in the nivolumab versus chemotherapy arm.

1.1.3 Rationale for Flat Dosing of Nivolumab

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

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Table 1.1.3-1 presents summary statistics of the estimated nivolumab steady-state trough, peak and time-averaged concentration (Cminss, Cmaxss, and Cavgss, respectively) in NSCLC subjects receiving 3 mg/kg, together with corresponding statistics of exposures predicted for a flat nivolumab dose of 240 mg. It should be noted that a dose of 240 mg nivolumab is identical to a dose of 3 mg/kg for subjects weighing 80 kg, which is the approximate median body weight of NSCLC subjects in the 3 phase 2 and 3 clinical studies of nivolumab monotherapy in NSCLC patients (CA209017, CA209057, and CA209063). As evident from the data presented in Table 1.1.3-1, the geometric mean values of Cminss, Cmaxss, and Cavgss with flat dosing are slightly (< 15%) higher than that produced by a 3 mg/kg dose, and the coefficient of variation (cv%) in these measures of exposure are only slightly (< 10%) greater than that of 3 mg/kg dosing.

Table 1.1.3-1: Summary Statistics of Nivolumab Steady-state Exposure

Nivolumab Dose	Cminss Geo. Mean [μg/mL] (cv %)	Cmaxss Geo. Mean [μg/mL] (cv %)	Cavgss Geo. Mean [μg/mL] (cv %)
240 mg	61.5 (44.6)	133.7 (35.0)	82.4 (38.2)
3 mg/kg	54.7 (41.9)	118.9 (31.8)	73.3 (35.6)

Nivolumab has been shown to be safe and well tolerated up to a dose level of 10 mg/kg, and the relationship between nivolumab exposure produced by 3 mg/kg and efficacy has been found to be relatively flat. Taken together, the PK, safety, and efficacy data indicate that the safety and efficacy profile of 240 mg nivolumab will be similar to that of 3 mg/kg nivolumab. Similarly, a flat dose of 360 mg corresponds to a dose of 4.5 mg/kg q3w, which is similar to the nivolumab doses evaluated in combination with chemotherapy in CA209012, ranging from 5-10 mg/kg q3w). The simulated steady state concentration at trough (Cminss), peak (Cmaxss), and average (Cavgss) with 360 mg are less than 10 mg/kg every 2 weeks. Thus, these regimens are expected to be safe and tolerable.

The PK and safety of nivolumab have been evaluated in the Asian population. The comparison of PK parameters in global and Japanese subjects suggests that the PK of nivolumab is similar in these populations. Nivolumab is shown to be safe and well tolerated in Japanese subjects. The similar PK and safety profile of nivolumab between global and Japanese subjects supports the use of similar dosing in the Asian population as is being used in global clinical studies.

Based on these clinical results, the monotherapy arm in CA209227 will be nivolumab monotherapy 240 mg every 2 weeks, and a dose of nivolumab 360 mg every 3 weeks will be used in the nivolumab plus chemotherapy arms.

Due to the smaller therapeutic window of the ipilimumab/nivolumab combination, nivolumab will be given in a weight based schedule when combined with ipilimumab.

1.1.4 Rationale for Platinum Doublet Chemotherapy in Comparator Arms

First-line treatment of advanced NSCLC is histology specific and consists of platinum-based chemotherapy doublets. For example, pemetrexed is approved in first-line in combination with

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cisplatin for locally advanced or metastatic non squamous NSCLC. This approval was based on a Phase III, randomized study that showed improved survival and decreased toxicity for pemetrexed combined with cisplatin in patients with non-squamous histology, in comparison to gemcitabine combined with cisplatin.[20] Pemetrexed has also been approved as continuation maintenance therapy in patients with non-squamous histology, who have not had progressive disease after four cycles of a first-line pemetrexed/platinum regimen. In contrast, gemcitabine in combination with cisplatin has been demonstrated to yield improved overall survival compared to pemetrexed/cisplatin in subjects with squamous NSCLC. In squamous NSCLC, carboplatin plus paclitaxel is an alternative standard of care preferred in some geographies.

Although some but not all meta-analyses and randomized studies have demonstrated that cisplatin-based regimens may produce improved survival compared to carboplatin-based regimens, many subjects are not ideal candidates for cisplatin due to its higher toxicity.[21]

In Parts 1A, 1B, and 2, subjects with *non-squamous* histology who are randomized to the comparator arm (Arms C, F, or H) may receive either of the following pemetrexed/platinum regimens, and they have the option for continuation of pemetrexed as maintenance therapy:

- Pemetrexed/cisplatin (4 cycles) ± pemetrexed maintenance
- Pemetrexed/carboplatin (4 cycles) ± pemetrexed maintenance

Note: The investigator must decide prior to the subject's randomization whether or not the subject will receive pemetrexed maintenance therapy, provided the subject is eligible for it.

In Part 1B, subjects with *squamous* histology randomized to the comparator arm (Arms C or F) may receive either of the following gemcitabine/platinum regimens:

- Gemcitabine/cisplatin (4 cycles)
- Gemcitabine/carboplatin (4 cycles)

In Part 2, subjects with *squamous* histology randomized to the comparator arm in part 2 (Arms I) will receive:

- Paclitaxel/carboplatin (4 cycles)

Using the paclitaxel/carboplatin regimen will generate additional data with an alternative platinum doublet, which is used more frequently in the U.S. and Japan. Gemcitabine-base combinations are more frequently used in Europe. However, prior data from CheckMate 012 suggest similar efficacy and safety when combining nivolumab with chemotherapy, regardless of the chemotherapy backbone.

1.1.5 Rationale for Nivolumab plus Platinum-Doublet Chemotherapy (Parts 1B and 2)

The interaction of a tumor with the immune system is complex. Tumors and the tumor microenvironment are known to express a variety of factors that impede a robust immune response

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from eliminating the tumor. Soluble and membrane-bound factors have been shown to inhibit the cytolytic activity of tumor infiltrating T-cells (e.g., PD-L1 expression; TGF-beta). In addition, some tumor-derived factors are able to enhance immune system counter-regulatory systems (e.g., increased T-regulatory cells). Finally, suboptimal tumor antigen delivery and presentation has been postulated as another mechanism by which tumors can successfully evade immune system recognition.

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

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

The safety profile of nivolumab plus platinum-doublet chemotherapy reflects additive toxicities of the individual agents, which were manageable using established safety guidelines (Table 1.1.5-1). The frequency of most immune-related select AEs was higher than what has been observed for nivolumab monotherapy. However, these treatment-related AEs, including pneumonitis, were effectively managed and did not lead to any deaths.

Table 1.1.5-1: Treatment-related AEs Reported in ≥ 10% of all NSCLC Subjects Treated with Nivolumab plus Platinum-based Chemotherapy

	Total (n=56)	
Treatment-related AE, n (%)	**All Grades**	**Grade 3/4**
Patients with any AE	53 (95)	25 (45)
Fatigue	40 (71)	3 (5)
Nausea	26 (46)	1 (2)
Decreased appetite	20 (36)	1 (2)
Alopecia	17 (30)	0
Anemia	15 (27)	2 (4)
Rash	14 (25)	2 (4)
Diarrhea	12 (21)	1 (2)
Arthralgia	12 (21)	0
Constipation	11 (20)	0
Peripheral neuropathy	11 (20)	0
Dysgeusia	8 (14)	0
Hypersensitivity	8 (14)	1 (2)

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Table 1.1.5-1: Treatment-related AEs Reported in ≥ 10% of all NSCLC Subjects Treated with Nivolumab plus Platinum-based Chemotherapy

	Total (n=56)	
Treatment-related AE, n (%)	**All Grades**	**Grade 3/4**
Vomiting	8 (14)	0
Mucosal inflammation	7 (12)	0
Myalgia	7 (12)	0
Pneumonitis	7 (12)	4 (7)
Infusion-related reaction	6 (11)	0
Leukopenia	6 (11)	0
Lymphopenia	6 (11)	0
Peripheral sensory neuropathy	6 (11)	0
Pruritus	6 (11)	0
Treatment related AEs leading to discontinuation	11(2)	

The observed response rates of nivolumab and chemotherapy (Table 1.1.5-2) were similar to that of platinum-doublet chemotherapy alone, though the duration of responses is longer. The median duration of response across all the nivolumab + chemotherapy cohorts was 27.3 weeks. The 1-year survival rate for all cohorts combined is 71%.

Table 1.1.5-2: Efficacy in First-Line Nivolumab + Chemotherapy

	Nivo/Gem/Cis (n=12)	Nivo/Pem/Cis (n=15)	Nivo/Pac/Carbo (n=29)	Nivo/Chemo (n=56)
ORR, n (%)	4 (33%)	7 (47%)	13 (45%)	24 (43%)
Median DOR (wks)	45	24.4	27.3	27.3
PFS rate at 24 wks	51%	71%	43%	52%
Median PFS (wks)	24.7	29.7	21.4	24.7
OS rate at 12 mos	50%	87%	72%	71%
OS rate at 18 mos	33%	60%	62%	55%
Median OS (wks)	50.5	83.4	89.6	83.4

Activity was also evaluated by PD-L1 expression and was observed in subjects with both PD-L1 expressing and non-expressing tumors (Table 1.1.5-3). Overall, 79% (44/56) of subjects had evaluable tumor samples. At the 1% expression level, the response rate was 48% and 43% for

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expressors and non-expressors, respectively. The 1-year overall survival was 70% and 76% for expressors and non-expressors, respectively.

Table 1.1.5-3: Efficacy in Nivolumab + Chemotherapy by PD-L1 Expression Level

	≥ 1% expression (n=23)	**< 1% expression (n=21)**
ORR, n (%)	11 (48)	9 (43)
Median duration of response (95% CI)	27.3 (12.3, 85.4)	25.4 (13.1, 56.7)
PFS rate at 24 wks (95% CI)	59 (34,77)	44 (22, 64)
Median PFS, wks	25.9	22.6
1-year OS rate, % (95% CI)	70 (47, 84)	76 (52, 89)
18-mo OS rate, % (95% CI)	57 (34, 74)	51 (28, 70)
Median OS, wks	88 (47, 118)	83 (53, 103)

Thus, the predictive value for PD-L1 expression appears to be attenuated in the nivolumab + chemotherapy setting, compared to what has been observed in the nivolumab monotherapy and nivolumab + ipilimumab settings. There appears to be no diminution in activity for patients with PD-L1 non-expressing tumors.

In addition, Keynote-021 (KN21), an open-label, phase 2 study that randomized previously untreated subjects with advanced NSCLC to pemetrexed plus carboplatin or pemetrexed plus carboplatin plus pembrolizumab, showed an improved response rate and PFS in subjects in the pembrolizumab arm.[22]The improved efficacy was substantial in subjects with high PD-L1 expressing tumors, but observed regardless of PD-L1 expression.

Thus, in part 1B nivolumab + chemotherapy will be evaluated in patients with PD-L1 non-expressing tumors, i.e., the subgroup where immunotherapy (without chemotherapy) appears to be least active in non-TMB selection population, and hence the highest medical need. Nonetheless, while the medical need is highest in PD-L1 non-expressing tumors, nivolumab plus chemotherapy may constitute a treatment option for some PD-L1 expressing patients. In part 2, nivolumab plus chemotherapy will be evaluated in a broader population than was evaluated in Part 1B. Subjects with stage IV NSCLC will be randomized to platinum-based chemotherapy with or without nivolumab, regardless of PD-L1 expression levels. Thus, Part 2 should be considered as an expansion of Part 1B, enrolling subjects with both PD-L1 expressing and non-expressing tumors, while also evaluating an additional platinum doublet, paclitaxel + carboplatin. Evaluation of multiple treatment options across a broad spectrum of PD-L1 expression in study CA209227 will help identify optimal treatment strategies for each patient.

The following nivolumab + chemotherapy schedules will be used in CA209227:

- Non-squamous histology (Part 1B, Arms F and G, and Part 2, Arms H and I)

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nivolumab + pemetrexed with cisplatin (4 cycles), followed by nivolumab + pemetrexed maintenance therapy for those without disease progression following combination therapy
nivolumab + pemetrexed with carboplatin (4 cycles), followed by nivolumab + pemetrexed maintenance therapy for those without disease progression following combination therapy

NOTE: The chemotherapy backbone for non-squamous histology will be the same in Parts 1B and 2 since pemetrexed-based therapies are a global standard of care.

- Squamous histology (Part 1B)
  nivolumab + gemcitabine with cisplatin (4 cycles)
  nivolumab + gemcitabine with carboplatin (4 cycles)
- Squamous histology (Part 2)
  nivolumab + carboplatin/paclitaxel (4 cycles), followed by nivolumab maintenance for those without progression following combination therapy

NOTE: As Part 2 is an expansion of Part 1B, further evaluating the effect of adding nivolumab to chemotherapy in subjects with both PD-L1 expressing tumors and non-expressing tumors, using carboplatin/paclitaxel as a chemotherapy backbone for subjects with squamous histology, will help generate data with an alternative standard of care in squamous NSCLC, which is preferred in some geographies.

As the PK of nivolumab is linear, the corresponding flat dose of nivolumab for an every 3-week schedule is 360 mg. The simulated steady state concentration at trough (C_{minss}), peak (C_{maxss}), and average (C_{avgss}) with 360 mg are less than 10 mg/kg every 2 weeks. Thus, these regimens are expected to be safe and tolerable.

1.1.6 Rationale for Shorter Infusion Times for Nivolumab and Ipilimumab

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

Previous clinical studies of nivolumab monotherapy and ipilimumab monotherapy and the combination of nivolumab and ipilimumab have used a 60 minute infusion duration for nivolumab and 90 minute infusion duration for ipilimumab (1-3 mg/kg dosing for both). However, both nivolumab and ipilimumab have been administered at up to 10 mg/kg with the same infusion duration:

- Nivolumab has been administered safely over 60 minutes at doses ranging up to 10 mg/kg safely over long treatment duration. In Study (CA209010, a Phase 2, randomized, double blinded, dose-ranging study of nivolumab in subjects with advanced/metastatic clear cell RCC) a dose association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg and 18.5% at 10 mg/kg). All the events were grade 1-2 and were manageable. An infusion duration of 30 minutes for 3 mg/kg, or 240 mg, or 360 mg is not expected to present any safety concerns compared to the prior experience at 10 mg/kg nivolumab dose infused over a 60 minute duration.

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

Of note, CA209153, a phase IIIb/IV safety study of nivolumab in subjects with metastatic NSCLC who have progressed during or after at least one prior systemic regimen, has used a 30 minute infusion in a cohort of subjects with no safety issues.

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

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

Accumulating clinical evidence indicates some subjects treated with immune system stimulating agents may develop progression of disease (by conventional response criteria) before demonstrating clinical objective responses and/or stable disease. This phenomenon was observed in approximately 10% of subjects in the Phase 1 study of nivolumab and also with ipilimumab monotherapy.[23] Two hypotheses have been put forth to explain this phenomenon. First, enhanced inflammation within tumors could lead to an increase in tumor size which would appear as enlarged index lesions and as newly visible small non-index lesions. Over time, both the malignant and inflammatory portions of the mass may then decrease leading to overt signs of clinical improvement. Alternatively, in some individuals, the kinetics of tumor growth may initially outpace anti-tumor immune activity. With sufficient time, the anti-tumor activity will dominate and become clinically apparent. Therefore for arms A, B, D, G and H, subjects will be allowed to continue study therapy after initial investigator-assessed RECIST 1.1 defined progression if they are assessed to be deriving clinical benefit and tolerating study drug (Section 4.5.7). Such subjects must discontinue study therapy upon evidence of further progression.

1.1.8 Rationale for Two Year Duration of Treatment

The optimal duration of immunotherapy is currently unknown. However, because immunotherapy engages the immune system to control the tumor, continuous treatment as is required with targeted agents or cytotoxic therapy may not be necessary. Accumulating evidence from different clinical trials in different tumors types with nivolumab or nivolumab combined to ipilimumab indicates that most of the responses are generally occurring early, with a median time to response of 2-4

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months including in patients with NSCLC,[5,7,24] and a recent analysis in a melanoma study suggests the majority of patients who discontinue nivolumab and/or ipilimumab for toxicity maintain disease control in the absence of further treatment[25]. Furthermore, melanoma patients who stop treatment with a PD-1 inhibitor at 2 years rarely recur,[26] and with ipilimumab a limited duration including only 4 induction doses resulted in long term survival in patients with metastatic melanoma, with a sustained plateau in survival starting at around year 2.[27] In previously treated NSCLC, while recent data suggest that 1 year of treatment may not be sufficient[28] PFS appears to plateau around 2 years regardless of whether treatment is continued, and 3 year survival is identical in studies where nivolumab is stopped at 2 years versus given until progression. Checkmate 003, a dose-escalation cohort expansion trial evaluating the safety and clinical activity of nivolumab in patients with advanced solid tumors, implemented stopping nivolumab monotherapy at 96 weeks (~ 2 years). The median follow-up was 60 months; among the 16 subjects enrolled in the NSCLC cohort 12 subjects were alive >5 years and did not receive further therapy after stopping nivolumab and remained progression free.[29] In CheckMate studies 017 and 057, subjects in the nivolumab arms received treatment until progression. In CheckMate 017, PFS at 2 and 3 years was 16% and 12% respectively, and in CheckMate 057 it was 12% and 10%. Overall survival in CheckMate 017 at 2 and 3 years was 23% and 16% respectively, and in CheckMate 057 it was 29% and 18%.[30]

For these reasons, in study CA209227, treatment with nivolumab or nivolumab with ipilimumab will be given for up to 24 months in the absence of disease progression or inacceptable toxicity. Chemotherapy will be given as per the study dosing schedule.

1.1.9 Rationale for Patient Population

1.1.9.1 Rationale for Exclusion of Subjects with EGFR Mutations or ALK Translocations (Parts 1 and 2)

As first-line standard of care for subjects with EGFR mutations and ALK translocations is targeted therapy rather than chemotherapy,[2] subjects known to have these abnormalities will be excluded from this study.

In addition, patients with EGFR mutations have a better prognosis, even in the absence of EGFR inhibitor therapy[31] and may have an improved response to chemotherapy compared to patients without EGFR mutations.[32] Patients with ALK translocations who are treated with chemotherapy appear to have similar PFS compared to patients without ALK translocations who are treated with chemotherapy.[33] Excluding subjects with these abnormalities will help to reduce the potentially confounding effects of these abnormalities on the study endpoints.

1.1.10 Rationale for Endpoints

1.1.10.1 Rationale for Co-Primary Endpoint of OS in Part 1 PD-L1+ and Primary Endpoint of OS in Part 2

Overall survival is a gold-standard for demonstrating clinical benefit in NSCLC standard and less influenced by variability measurement, scanning frequency, and other issues interfering with accurately measuring PFS.

Underlying assumptions for overall survival in the control arms:

Prior phase 3 randomized studies of platinum double chemotherapy have documented median OS of 9-11 months. More recent randomized studies with maintenance therapy with bevacizumab or pemetrexed in non-squamous NSCLC patients have further improved median OS to ~ 13.9 months (Section 1.5.3). As this study will enroll NSCLC patients regardless of histology, we anticipate that about 80% subjects will have non-squamous histology, and that about half of these subjects are expected to receive continuation maintenance therapy. Most recently, Checkmate 026 showed a median OS of 13.7 months in subjects with ≥ 1% tumor PD-L1 expression treated with similar platinum based doublets, with no major differences at higher expression levels (PD-L1 negative subjects were not evaluated). For these reasons, the median OS is estimated to be 13.3 months for the comparator arm (Arms C and F).

1.1.10.2 Rationale for Co-Primary Endpoint of PFS in Part 1 TMB high

PFS was chosen as co-primary endpoint to measure benefit from nivolumab+ipilimumab versus chemotherapy in a TMB high population based on the expected smaller sample size of the TMB high population (compared to the PD-L1+ population) which will not provide full power to detect a survival benefit. Furthermore, in 026, while the patients with highest tertile of TMB derived a PFS benefit from nivolumab monotherapy versus chemotherapy, median OS was considerably longer than historical controls in both arms, perhaps due to the high frequency of cross over in the TMB high subgroup (65%). OS in the TMB high subgroup will be assessed as a secondary endpoint.

Underlying assumptions for PFS:

Assumptions for PFS are based on subgroup analyses from Checkmate 026, which showed in the nivolumab group, subjects with high TMB had improved PFS versus chemotherapy. The median PFS in the nivolumab arm was 9.7 months compared to 5.8 months in the chemotherapy arm (HR = 0.62; 95% CI: 0.38, 1.00). Among subjects with low or medium TMB, the median PFS was 4.1 months in the nivolumab arm versus 6.9 months in the chemotherapy arm (HR = 1.82 ;95% CI: 1.30, 2.55).[34]

1.1.10.3 Rationale for Part 2 study Endpoints

Emerging data across multiple studies consistently demonstrate the role of PD-L1 therapy in combination with conventional platinum based chemotherapy in first line NSCLC without EGFR or ALK mutations. Although the clinical benefit versus chemotherapy was reported across all histologies, progression and overall survival improvement was more pronounced in the non-squamous subtype.[35,36]

Therefore, in order to appropriately assess the activity of nivolumab + chemotherapy versus chemotherapy, hierarchical hypothesis testing will be used in Part 2 to test whether the combination is superior to chemotherapy in terms of OS improvement, first in subjects with non-squamous histology, and then in the Intent-to-Treat (ITT) population.

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1.1.11 Rationale for Open Label Design

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

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

1.1.12 Rationale for Tumor Mutation Burden

Tumor Mutational Burden (TMB) refers to the total number of nonsynonymous somatic mutations that exist within a tumor's genome. A subset of these mutations, termed neo-antigens, may result in an expressed protein that is not recognized by the host's immune system as self, and therefore has the potential to be immunogenic, leading to an anti-tumor immune-mediated response. Tumors with a high mutation burden may have a higher rate of neo-antigens which, in principle, would be expected to be more immunogenic than tumors with comparatively low mutation burden. Therefore, high TMB has been hypothesized to correlate with improved efficacy in patients treated with I-O therapies. This hypothesis has been supported in multiple publications across IO therapies, tumor types, and lines of treatment. The first published study of TMB as a biomarker of clinical outcomes was reported by Snyder et al (2014), where high TMB was found to be associated with efficacy in metastatic melanoma patients treated with anti-CTLA-4 therapy. Further studies by Rizvi et al (2015) reported TMB as a biomarker of pembrolizumab efficacy in second-line NSCLC patients. Additional studies of pembrolizumab and atezolizumab in NSCLC have been generally consistent with these results.[37]

Recently, TMB was evaluated in an exploratory post hoc analysis in the BMS-sponsored first line NSCLC study, CheckMate 026, which represents the first Phase III study to demonstrate the impact of TMB on efficacy of a PD-1/L1 inhibitor.[16] This analysis demonstrated that in patients with high TMB, ORR was numerically higher in the nivolumab arm versus the chemotherapy arm (47% vs. 28%) and median PFS was longer in the nivolumab arm compared to the chemotherapy arm (9.7 vs. 5.8 mo., HR 0.62; 95% CI 0.38, 1.00). OS was notable, though similar (18.3 vs. 18.8 mo. and 1 year OS rates of 64% vs 60%, respectively), between the arms in patients with high TMB, although of note, 68% of patients in the chemotherapy arm received subsequent nivolumab. Interestingly, the ORR and mPFS rates observed in the high TMB subgroup within CheckMate 026 were similar to those reported in the first line NSCLC study of pembrolizumab (Keynote-024), where ORR and mPFS were 45% and 10.3 months, respectively, in patients with ≥50% PD-L1 expression treated with pembrolizumab monotherapy.[38]

Thus, the available data to date suggest that, in addition to PD-L1, TMB is also a biomarker of clinical efficacy to IO therapy.

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1.2 Research Hypotheses (Part 1)

- In chemotherapy-naïve subjects with stage IV or recurrent PD-L1 expressing NSCLC, the administration of nivolumab in combination with ipilimumab will improve overall survival (OS) compared with platinum-doublet chemotherapy.
- In chemotherapy-naïve subjects with stage IV or recurrent NSCLC with high tumor mutation burden at baseline and regardless of PD-L1 status, the administration of nivolumab in combination with ipilimumab, will improve PFS compared with platinum-doublet chemotherapy.

1.3 Research Hypotheses (Part 2)

- In chemotherapy-naïve subjects with stage IV or recurrent NSCLC irrespective of PD-L1 expression levels, the administration of nivolumab in combination with platinum-doublet chemotherapy, will improve OS compared with platinum-doublet chemotherapy.

1.4 Objectives

1.4.1 Part 1

1.4.1.1 Primary Objectives

In subjects with previously untreated stage IV or recurrent NSCLC:

- Subjects with PD-L1 expressing tumors: To compare overall survival (OS) of nivolumab in combination with ipilimumab (Arm B) to platinum-doublet chemotherapy (Arm C) in subjects whose tumors have ≥ 1% PD-L1 expression
- Subjects with high baseline tumor mutation burden: To compare progression-free survival (PFS based on BICR assessment) of nivolumab in combination with ipilimumab (Arms B plus D) to platinum-doublet chemotherapy (Arms C plus F) regardless PD-L1 expression level

1.4.1.2 Secondary Objectives

In subjects with previously untreated stage IV or recurrent NSCLC:

- Subjects depending on tumoral PD-L1 expression (these objectives will be hierarchically tested if the co-primary objective of OS in subjects with PD-L1 expressing tumors is positive):
  - To compare PFS, based on BICR assessment, of nivolumab in combination with platinum-doublet chemotherapy (Arm G), to platinum-doublet chemotherapy (Arm F) in subjects whose tumors do not express PD-L1 (<1%)
  - To compare OS of nivolumab in combination with platinum-doublet chemotherapy (Arm G), to platinum-doublet chemotherapy (Arm F) in subjects whose tumors do not express PD-L1 (<1%)
  - To compare OS of nivolumab monotherapy (Arm A) to platinum-doublet chemotherapy (Arm C) in subjects whose tumors have ≥ 50% PD-L1 expression

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- Subjects with high baseline tumor mutation burden (these objectives will be hierarchically tested if the co-primary objective of PFS in subjects with high TMB tumors is positive):
    - To compare PFS (based on BICR assessment) of nivolumab monotherapy (Arm A) to platinum-doublet chemotherapy (Arm C) in subjects whose tumors have ≥ 1% PD-L1 expression and with high baseline tumor mutation burden
    - To compare OS of nivolumab in combination with ipilimumab (Arms B plus D) to platinum-doublet chemotherapy (Arms C plus F) in subjects with high baseline tumor mutation burden regardless PD-L1 expression level
    - To compare OS of nivolumab (Arm A) to platinum-doublet chemotherapy (Arm C) in subjects whose tumors have ≥ 1% PD-L1 expression and with high baseline tumor mutation burden

1.4.2 Part 2

1.4.2.1 Primary Objective

In subjects with previously untreated stage IV or recurrent NSCLC irrespective of PD-L1 expressing levels:

- In subjects with non-squamous histology (at randomization as stratified):
    - To compare OS of nivolumab in combination with platinum-doublet chemotherapy (Arm H), to platinum-doublet chemotherapy (Arm I)

1.4.2.2 Secondary Objectives

In subjects with previously untreated stage IV or recurrent NSCLC irrespective of PD-L1 expressing levels:

- In all randomized subjects (ITT population):
    - To compare OS of nivolumab in combination with platinum-doublet chemotherapy (Arm H), to platinum-doublet chemotherapy (Arm I). (This objective will be hierarchically tested if the primary objective of OS in subjects with non-squamous histology tumors is positive).

The following are also secondary objectives but not part of the hierarchy:

- In subjects with non-squamous histology:
    - To compare the OS of nivolumab in combination with platinum-doublet chemotherapy (Arm H), among high baseline tumor mutation burden (≥ 10 mut/Mb) subgroup
    - To compare the PFS, based on BICR assessment, of nivolumab in combination with platinum-doublet chemotherapy (Arm H), to platinum-doublet chemotherapy (Arm I)
    - To compare the ORR (BICR assessment) of nivolumab in combination with platinum doublet chemotherapy (Arm H), to platinum-doublet chemotherapy (Arm I)

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- To evaluate efficacy (OS, PFS, and ORR) by PD-L1 expressing levels for nivolumab in combination with platinum-doublet chemotherapy (Arm H) and platinum-doublet chemotherapy (Arm I)
- To evaluate efficacy (OS, PFS, and ORR) by TMB levels for nivolumab in combination with platinum-doublet chemotherapy (Arm H) and platinum-doublet chemotherapy (Arm I)

- In all randomized subjects (ITT population):
  - In subjects with high baseline tumor mutation burden (≥ 10 mut/Mb): To compare the OS of nivolumab in combination with platinum-doublet chemotherapy (Arm H)
  - To compare the PFS, based on BICR assessment, of nivolumab in combination with platinum-doublet chemotherapy (Arm H), to platinum-doublet chemotherapy (Arm I)
  - To compare the ORR (BICR assessment) of nivolumab in combination with platinum-doublet chemotherapy (Arm H), to platinum-doublet chemotherapy (Arm I)
  - To evaluate efficacy (OS, PFS, and ORR) by PD-L1 expressing levels for nivolumab in combination with platinum-doublet chemotherapy (Arm H) and platinum-doublet chemotherapy (Arm I)
  - To evaluate efficacy (OS, PFS, and ORR) by TMB levels for nivolumab in combination with platinum-doublet chemotherapy (Arm H) and platinum-doublet chemotherapy (Arm I)

1.4.3 Exploratory Objectives (Parts 1 and 2)

[redacted]

- To evaluate OS, PFS per BICR assessment, and ORR per BICR assessment, of nivolumab monotherapy (Arm A), nivolumab in combination with ipilimumab (Arms B and D), nivolumab in combination with platinum-doublet chemotherapy (Arm G) and platinum-doublet chemotherapy (Arms C and F)
- To assess PFS after next line of treatment (PFS2) in each arm
- To assess the overall safety and tolerability of nivolumab monotherapy (Arm A), nivolumab in combination with ipilimumab (Arms B and D), and nivolumab in combination with platinum-doublet chemotherapy (Arms G and H), compared to platinum-doublet chemotherapy (Arms C, F, and I)
- To characterize pharmacokinetics of nivolumab alone (Arm A), nivolumab in combination with ipilimumab (Arms B and D), or nivolumab in combination with platinum-doublet chemotherapy (Arms G and H) and explore exposure-safety and exposure-efficacy relationships

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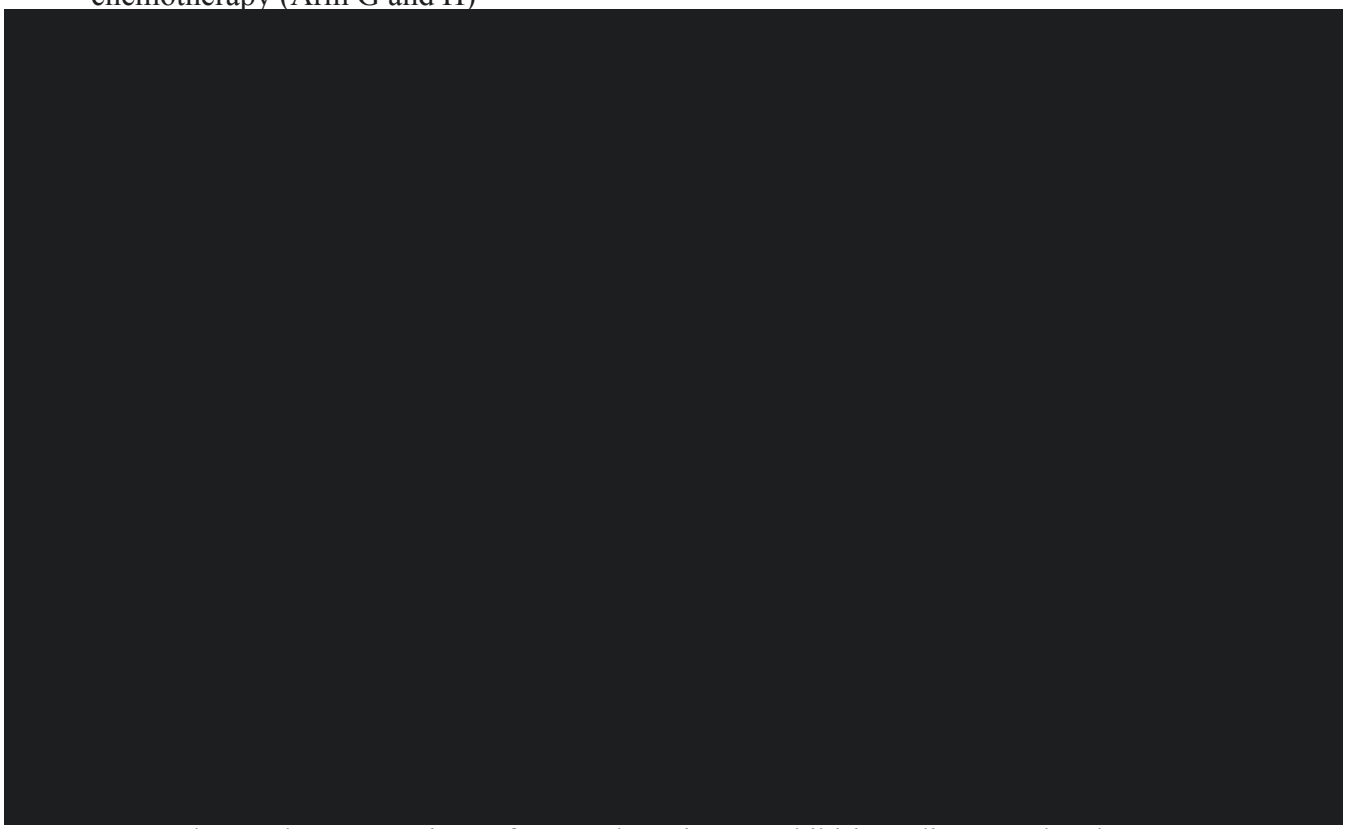
- To characterize immunogenicity of nivolumab alone (Arm A), nivolumab in combination with ipilimumab (Arms B and D), or nivolumab in combination with platinum-doublet chemotherapy (Arm G and H)



- To evaluate the proportion of treated patients exhibiting disease-related symptom deterioration by 12 weeks, as measured by the Lung Cancer Symptom Score (LCSS) average symptom burden index (ASBI)
- To evaluate the time to deterioration in symptoms, as measured by the LCSS ASBI
- To assess health utility (quality of life) using the EQ-5D index and overall health status using the EQ-5D visual analogue scale (VAS)

1.5 Product Development Background

Nivolumab is in clinical development for the treatment of subjects with NSCLC, renal cell carcinoma (RCC), melanoma, and other tumors (e.g., glioblastoma multiforme, Hodgkin's lymphoma, small cell lung cancer).

The initial U.S. approval for nivolumab (Opdivo®) was in 2014. Opdivo® is currently approved for the following:

- BRAF V600 wild-type unresectable or metastatic melanoma, as a single agent
- BRAF V600 mutation-positive unresectable or metastatic melanoma, as a single agent
- Unresectable or metastatic melanoma, in combination with ipilimumab
- Metastatic non-small cell lung cancer and progression on or after platinum-based chemotherapy
- Advanced renal cell carcinoma who have received prior anti-angiogenic therapy

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- Classical Hodgkin lymphoma that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin
- Recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy

Opdivo® is also approved in the European Union, Japan and elsewhere in the world.

This study, CA209227, will evaluate the efficacy and safety of nivolumab monotherapy, and nivolumab in combination with ipilimumab, as first-line therapy in patients with stage IV or recurrent NSCLC.

1.5.1 Mechanism of Action of Nivolumab

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses.[39, 40, 41] Support for the role of immunosurveillance in NSCLC is suggested in retrospective analyses demonstrating a correlation between tumor infiltrating lymphocytes in surgically resected specimens and recurrence free survival.[42,43,44] Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system.

T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor (TCR).[45] Collectively, these signals govern the balance between T-cell activation and tolerance to antigens. PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA-4, ICOS, and BTLA.[46] PD-1 signaling has been shown to inhibit CD-28-mediated upregulation of IL-2, IL-10, IL-13, interferon-γ (IFN-γ) and Bcl-xL. PD-1 expression also been noted to inhibit T cell activation, and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes.[47] These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self antigens.

In vitro, nivolumab binds to PD-1 with high affinity (EC50 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (IC50 ± 1 nM). BMS-936558 binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4 and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both

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proliferation and IFN-γ release in the mixed lymphocyte reaction (MLR). Using a CMV re-stimulation assay with human PBMC, the effect of nivolumab on antigen specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV specific memory T cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and result in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[48]

1.5.2 Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4) and Ipilimumab

CTLA-4, an activation-induced T-cell surface molecule, is a member of the CD28:B7 immunoglobulin superfamily that competes with CD28 for B7. CTLA-4 mediated signals are inhibitory and turn off T cell-dependent immune responses.[49, 50]

Ipilimumab is a fully human monoclonal IgG1κ that binds to the CTLA-4 antigen expressed on a subset of T cells from human and nonhuman primates. The proposed mechanism of action for ipilimumab is interference of the interaction of CTLA-4 with B7 molecules on APCs, with subsequent blockade of the inhibitory modulation of T-cell activation promoted by the CTLA 4/B7 interaction.

1.5.3 Non-Small Cell Lung Cancer (NSCLC) - Background and Treatments of First-Line Therapy

Lung cancer is the leading cause of cancer and cancer-related deaths globally, accounting for 1.8 million new cases and 1.6 million deaths worldwide in 2012.[51] Between 2004 and 2010, according to the SEER database, the overall 5 year survival rate was 21.4%.[52] The majority of subjects were diagnosed with advanced or metastatic disease. Prognosis for these patients remains dismal, with 5-year survival rates of < 5%. Approximately 85% of lung cancer is NSCLC, and of these, approximately 80% are non-squamous, and 20% are squamous histology.

The use of platinum-based chemotherapy doublets, given for up to 6 cycles, is standard-of-care for patients with newly diagnosed advanced or metastatic NSCLC who do not have EGFR mutation or ALK translocation. Current first-line chemotherapy doublets include cisplatin or carboplatin in combination with antimicrotubule agents, gemcitabine, or pemetrexed.

Overall response rates with these platinum doublets is approximately 25%. Progression-free survival (PFS) has remained about 4 to 5.5 months, with overall survival (OS) about 9 to 11 months. [20]

It has been recognized that response and outcome after treatment may vary according to histologic subtype. The platinum doublet of pemetrexed/cisplatin improves PFS and OS compared to gemcitabine/cisplatin in subjects with non-squamous histology NSCLC; gemcitabine/cisplatin improves OS compared to pemetrexed/cisplatin in subjects with squamous cell histology.[20] In the PARAMOUNT study, pemetrexed was demonstrated to improve PFS and OS, when continued as maintenance therapy in patients with non-squamous NSCLC which did not progress, after completion of induction treatment with pemetrexed/cisplatin.[53] However, there have been no

substantial improvements in long term survival, making NSCLC a persistent area of high unmet medical need.

The major adverse events related to platinum doublet chemotherapy regimens are primarily hematologic. For example, with gemcitabine/cisplatin, the rate of Grade 3/4 neutropenia is 27%; the rate of Grade 3/4 anemia is 10%; and the rate of Grade 3/4 thrombocytopenia is 13%. With pemetrexed/cisplatin, the rate of Grade 3/4 neutopenia is 15%; the rate of Grade 3/4 anemia is 6%, and the rate of Grade 3/4 thrombocytopenia is 4%.[20]

Non-hematologic adverse events vary according to the specific platinum doublet. For example, those related to gemcitabine/cisplatin include alopecia (21%, all grades), vomiting (6%, Grade 3/4), fatigue (5%, Grade 3/4), and febrile neutropenia (4%, Grade 3/4).[20] Common non hematologic adverse events associated with paclitaxel/carboplatin include neuropathy (18%, Grade 2/3), arthralgia (6%, Grade 3/4), fatigue (5%, Grade 3/4), and febrile neutropenia (3%, Grade 3/4).[54, 18]

Besides histology, the choice of platinum doublet for any individual NSCLC patient may depend on the toxicities associated with different doublets.

In one recently reported study,[38] an anti-PD1 antibody, pembrolizumab showed improved efficacy compared to chemotherapy as first-line treatment in patients with advanced NSCLC and PD-L1 expression on at least 50% of tumor cells.

1.5.3.1 Cisplatin

Cisplatin is a platinum-based drug that is used in NSCLC. Cisplatin is administered intravenously at a dose of 75 mg/m² over 30 to 120 minutes after gemcitabine or over 120 minutes after pemetrexed. Subjects who are receiving cisplatin must be monitored for nephrotoxicity, ototoxicity and neuropathy in addition to myelosuppression. Caution must be observed in cases of nausea, vomiting and dehydration. Dose modifications according to toxicities are noted in Sections 4.5.4.2, 4.5.4.3, and 4.5.4.4. For additional information regarding risks, as well as preparation and storage information, please consult the local prescribing information for cisplatin.

1.5.3.2 Carboplatin

Carboplatin is a platinum-based drug that is used in combination with a taxane, gemcitabine, or pemetrexed for treatment of NSCLC. Carboplatin is administered intravenously at a dose of AUC 5 or 6 mg/mL*min (per Calvert formula) over 15 to 30 minutes after the use of paclitaxel[55] or pemetrexed.[56] Carboplatin may also be given at a dose of AUC 5 or 6 mg/mL*min (per Calvert formula) with gemcitabine[57] or pemetrexed.[58,59] Subjects who are receiving carboplatin must be monitored for myelosuppression and anaphylaxis. Dose modifications according to toxicities are noted in Sections 4.5.4.2, 4.5.4.3, and 4.5.4.4. For preparation and storage, please consult the prescribing information for carboplatin.

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1.5.3.3 Gemcitabine

Gemcitabine is indicated in combination with cisplatin in first-line treatment of inoperable, locally advanced (Stages IIIA or IIIB) or metastatic (Stage IV) NSCLC. Using the three week schedule, gemcitabine is administered intravenously at a dose of 1,000 or 1,250 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle. Cisplatin should be administered 30 minutes after gemcitabine on Day 1 only at a dose of 75 mg/m².

Gemcitabine may also be given at a dose of 1000 mg/ m² over 30 minutes on Days 1 and 8 for each 21-day cycle, in combination with carboplatin at AUC 5 mg/mL*min (per Calvert formula), as first-line treatment of advanced NSCLC.[57]

Dose adjustments for hematologic toxicity may be required for gemcitabine and cisplatin (individually). Gemcitabine dosage adjustment for hematologic toxicities based upon the granulocyte and platelet counts on the day of treatment. Subjects receiving gemcitabine should be monitored prior to each dose using complete blood counts (CBC). If marrow suppression is noted, dose modifications are noted in Section 4.5.4.3. For non-hematologic toxicities, other than alopecia and nausea, dose modifications should be considered for both gemcitabine and cisplatin (Section 4.5.4.4). For additional information regarding risks, as well as preparation and storage information, please consult the local prescribing information for gemcitabine.

1.5.3.4 Pemetrexed

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

The premedication regimen for pemetrexed includes folic acid and vitamin B12 as well as dexamethasone or equivalent to reduce cutaneous reactions. Subjects receiving pemetrexed should be monitored prior to each dose using CBC and renal function tests. If marrow suppression is noted, dose modifications are noted in Sections 4.5.4.2, 4.5.4.3, and 4.5.4.4. For renal toxicity, pemetrexed should be held when the creatinine clearance (CrCl) < 45 mL/minute. Caution should be used among subjects who are receiving non-steroidal anti-inflammatory drugs (NSAIDs) and who have mild to moderate renal insufficiency (CrCl between 45 and 79 mL/minute). Caution should also be used when nephrotoxic drugs are administered with pemetrexed. For additional information regarding premedication regimen, risks, as well as preparation and storage information, please consult the local prescribing information for pemetrexed.

1.5.3.5 Paclitaxel (Part 2 only)

Paclitaxel is a taxane that is indicated in combination with cisplatin in first-line treatment for inoperable, locally advanced (Stages IIIA and IIIB) or metastatic (Stage IV) NSCLC. Paclitaxel is also commonly used in combination with carboplatin. Paclitaxel is administered intravenously at

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200 mg/m^2 over 3 hours, and premedication using diphenhydramine (or equivalent) and dexamethasone (or equivalent) is required. Subjects must be observed for hypersensitivity reactions, myelosuppression, and neuropathy. Dose modifications according to toxicities are noted in Sections 4.5.4.2, 4.5.4.3, and 4.5.4.4. For additional information regarding risks, please consult the local prescribing information for paclitaxel. For information related to storage and preparation, please refer to the clinical supply labels or the appropriate package insert/summary of product characteristics (SmPC).

1.5.4 Nivolumab Combined With Ipilimumab

In CA209012, the combination of nivolumab and ipilimumab has been studied as first line therapy for subjects with previously untreated stage IV or recurrent NSCLC at several different dose and schedules (Section 1.1.1). As of 17 March 2015, 80 patients have been treated with this combination in the original cohorts (arms G, H, I, J, and N). At least one AE, regardless of causality, was reported in 100% of subjects these cohorts. The most common (reported at > 15% incidence) treatment related AEs (any Grade %; Grade 3-4 %: 82; 43) are fatigue (40; 4), diarrhea (30; 6), rash (28; 8), decreased appetite (19; 0), lipase increased (15; 8), and nausea (15; 1).

The majority of AEs leading to discontinuation (regardless of causality) were Grade 3 or 4 (reported in 17 of 80 subjects, 21%). Grade 3 events included pneumonitis, ALT increased, AST increased, colitis, diarrhea, ulcerative colitis, delayed gastric emptying, Miller Fisher syndrome, allergic nephritis, and rash. One subject discontinued due to Grade 4 event of ALT increased, and 2 subjects discontinued for AST increased. One patient died from pulmonary hemorrhage.

An additional 117 patients have been treated in the newer 3 cohorts, and the safety profile appears much improved. Only 8% of subjects have discontinued treatment due to a treatment related AE, a rate similar to what has been observed with nivolumab monotherapy; 31% have experienced grade 3-4 treatment-related AEs.

Table 1.5.4-1: First-Line Nivolumab + Ipilimumab Safety Summary

	Treatment-Related AEs, %	Treatment-Related AEs leading to discontinuation, %
Nivo 1 Q2W + Ipi 1 Q6W (n=40)		
Any Grade	73	8
Grade 3-4	35	8
Nivo 3 Q2W + Ipi 1 Q12W (n=38)		
Any Grade	74	5
Grade 3-4	29	3
Nivo 3 Q2W + Ipi 1 Q6W (n=39)		
Any Grade	69	10
Grade 3-4	28	10

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Based on these data and the efficacy data (Table 1.1.1-2 and Table 1.1.1-3), the nivolumab 3 mg/kg q2w with ipilimumab 1 mg/kg q6w (arm Q) schedule will be evaluated in CA209227.

1.6 Overall Risk/Benefit Assessment

1.6.1 Overall Risk/Benefit Assessment for Part 1

Subjects with newly diagnosed metastatic or recurrent NSCLC represent a great unmet need. The clinical activity of nivolumab and nivolumab plus ipilimumab observed to date in NSCLC, including two positive phase 3 studies demonstrating prolonged survival with nivolumab monotherapy compared to docetaxel in squamous and non-squamous NSCLC after platinum failure, suggests the potential for improved clinical outcomes also in a first-line setting. CA209017 showed that patients with squamous NSCLC benefited from nivolumab treatment regardless of PD-L1 status, though point estimates of efficacy measures suggested a slightly greater treatment effect in subjects with PD-L1 expressing tumors, compared to PD-L1 non-expressing tumors, across all cut-off values. CA209057 (non-squamous NSCLC) study demonstrated overall survival was superior for subjects receiving nivolumab compared to those receiving docetaxel. In this study, interaction p-values reported for PD-L1 expression subgroups by each of the pre-defined expression levels suggested a clinically important signal of a predictive association. Based on these data, study CA209227 allows only subjects with PD-L1 expressing tumors to be randomized to nivolumab monotherapy (Arm A).

The potential benefit of combination immunotherapy with nivolumab plus ipilimumab, or nivolumab plus platinum-doublet chemotherapy over standard-of-care platinum-based first-line chemotherapy is not yet known. CheckMate 026 demonstrated that the median OS with nivolumab is similar to platinum-doublet chemotherapy in patients with PD-L1 expressing tumors at the ≥ 1% level (13.7 months versus 13.8 months). The platinum-based chemotherapy regimens have similar clinical activity and well described safety profiles, characterized by myelosuppression and other regimen-specific non-hematologic toxicities, such as peripheral neuropathy, nausea/vomiting, and renal impairment. The safety profile of nivolumab plus platinum-doublet chemotherapy reflects additive toxicities of the individual agents, which were manageable using established safety guidelines. The frequency of most immune-related, select AEs was higher with nivolumab plus platinum-doublet chemotherapy in CA209-012 compared to, than previously reported with nivolumab monotherapy. However, these treatment-related AEs, including pneumonitis, were effectively managed and did not lead to any deaths.

The safety profile of nivolumab and nivolumab plus ipilimumab is characterized by immune-related toxicities, such as diarrhea, rash, pneumonitis, liver toxicity, and endocrinopathies.[60] The frequencies and intensities of these events in the combination are variable and depend on the specific doses and schedule used (Section 1.1.1). In the dosing schedules selected, these events were mostly low grade and manageable with the use of corticosteroids. Nivolumab and ipilimumab combination therapy has shown improved efficacy over either agent alone in melanoma.

In order to assess the potential benefit of nivolumab monotherapy, nivolumab plus ipilimumab, and nivolumab plus platinum-doublet chemotherapy in the treatment of patients with both PD-L1

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expressing and PD-L1 non-expressing advanced NSCLC compared to standard-of-care platinum-based first-line chemotherapy, a randomized trial will be performed. Subjects with PD-L1 expressing and PD-L1 non-expressing tumors will be randomized and assessed separately. Those with PD-L1 expressing tumors will be randomized to 1 of 3 arms: nivolumab monotherapy (Arm A), nivolumab plus ipilimumab (Arm B), or platinum doublet chemotherapy (Arm C). Those with PD-L1 non-expressing tumors will be randomized to 1 of 3 arms: nivolumab plus ipilimumab (Arm D), nivolumab plus platinum-doublet chemotherapy (Arm G), or platinum doublet chemotherapy (Arm F). Contemporaneous enrolment and randomization of the PD-L1+ and - arms allows for pooling of arms with the same treatment, to assess benefit in a TMB high population, regardless of PD-L1 expression.

1.6.2 Overall Risk/Benefit Assessment for Part 2

The potential benefit of nivolumab in combination with platinum-doublet chemotherapy over standard-of-care platinum-based first-line chemotherapy is supported by both CheckMate 012 as well as data with other PD-1 inhibitors, e.g. pembrolizumab in Keynote 021. The response rate observed from the two studies ranges from 33% to 55% regardless of PD-L1 expression levels. In KN021, which to date is the only randomized study, albeit with a very small sample size, the addition of a PD-1 inhibitor significantly increased ORR and prolonged PFS.[22] All published data to date indicate that a similar magnitude of benefit is observed with IO/chemo combinations regardless of PD-L1 expression level. Together, these data suggest that addition of nivolumab to platinum-doublet chemotherapy could provide benefit over doublet alone in a broad population of patients. The platinum-based chemotherapy regimens have similar clinical activity and well described safety profiles, characterized by myelosuppression and other regimen-specific non-hematologic toxicities, such as peripheral neuropathy, nausea/vomiting, and renal impairment. The safety profile of PD-1 agent plus platinum-doublet chemotherapy reflects additive toxicities of the individual agents, which were manageable using established safety guidelines. The frequency of most immune-related, select AEs was higher with nivolumab/pembrolizumab plus platinum-doublet chemotherapy compared to platinum-doublet. However, these treatment-related AEs, including pneumonitis, were effectively managed and did not lead to any deaths.

In order to assess the potential benefit of nivolumab plus platinum-doublet chemotherapy in the treatment of all patients with advanced NSCLC compared to standard-of-care platinum-based first-line chemotherapy, the Part 2 of the study will randomize all subjects into 1 of 2 arms: nivolumab plus platinum-doublet chemotherapy (Arm H), or platinum doublet chemotherapy (Arm I) irrespective of PD-1 expression levels.

To assure an ongoing favorable risk/benefit assessment for subjects enrolled onto CA209227, an independent Data Monitoring Committee (DMC) will be utilized to monitor the safety and clinical activity of the treatments throughout the conduct of the trial, until the primary end-point for each sub study is reached.

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2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

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

The study will be conducted in compliance with the protocol. The protocol 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 (e.g., 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 (e.g., 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 (e.g., 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 (i.e., 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.

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Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.

Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.

If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.

Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

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

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

Subjects unable to give their written consent (e.g., 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.

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3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is an open label, randomized, Phase 3 study in adult (≥ 18 years) male and female subjects, with stage IV or recurrent non-small cell lung cancer, PD-L1 expressing or non-expressing, previously untreated for advanced disease. The study has two parts: Part 1 (Part 1A for subjects with PD-L1 tumors and Part 1B for subjects with PD-L1 non-expressing tumors) and Part 2 for subjects regardless of tumor PD-L1 expression level.

PD-L1 status will be determined by immunohistochemical (IHC) staining of PD-L1 protein in the submitted tumor sample prior to randomization.

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 progression or treatment discontinuation, whichever occurs later. Subjects receiving nivolumab (Arms A, G, H) or nivolumab plus ipilimumab (Arms B and D) beyond investigator-assessed progression must also continue tumor assessments until such treatment has been discontinued.

Tumor assessment should also continue beyond the 2 year duration of therapy with nivolumab +/- ipilimumab for patients with no documented BIRC progression.

3.1.1 Part 1 Design

Subjects will first be assessed for PD-L1 expression, using ≥ 1% expression level, and categorized into 2 separate groups, PD-L1 expressing and PD-L1 non-expressing. PD-L1 status will be determined by immunohistochemical (IHC) staining of PD-L1 protein in the submitted tumor sample prior to randomization:

- PD-L1 expressing (≥ 1% tumor cell membrane staining in a minimum of a hundred evaluable tumor cells) vs
- PD-L1 non- expressing (< 1% tumor cell membrane staining in a minimum of a hundred evaluable tumor cells)

Subjects within each group will be stratified by histology:

- Squamous vs
- Non-squamous

Subjects categorized as PD-L1 expressing (Part 1A) will be randomized and treated with one of the following open-label treatments:

- **Arm A**: Nivolumab 240 mg administered IV over 30 minutes every 2 weeks until disease progression or unacceptable toxicity for up to 2 years. Nivolumab treatment beyond initial investigator-assessed RECIST 1.1 defined progression is permitted if the subject has investigator assessed clinical benefit and is tolerating nivolumab, as specified in Section 4.5.7.
- **Arm B**: 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

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progression, unacceptable toxicity, or other reasons specified in the protocol, for up to 2 years. Treatment beyond initial investigator-assessed RECIST 1.1 defined progression is permitted if the subject has investigator assessed clinical benefit and is tolerating nivolumab, as specified in Section 4.5.7.

- **Arm C**: Platinum-doublet chemotherapy administered in 3-week cycles for up to a maximum of 4 cycles of IV chemotherapy. Chemotherapy treatment will continue until disease progression, unacceptable toxicity or completion of the 4 cycles, whichever comes first. Choice of chemotherapy regimens is dependent on NSCLC histology.
  Squamous cell:
  Gemcitabine (1000 or 1250 mg/m^2) with cisplatin (75 mg/m^2). Gemcitabine administered on Day 1 and Day 8 of each cycle; or
  Gemcitabine (1000 mg/m^2) with carboplatin (AUC 5). Gemcitabine administered Day 1 and Day 8 of each cycle
  Non-squamous cell:
  Pemetrexed (500 mg/m^2) with cisplatin (75 mg/m^2) administered on Day 1 of each cycle, or
  Pemetrexed (500 mg/m^2) carboplatin (AUC 5 or 6) administered on Day 1 of each cycle

Note: Subjects with non-squamous histology who have stable disease or response after 4 cycles are permitted to continue pemetrexed alone as maintenance therapy until disease progression or unacceptable toxicity. **The investigator must decide prior to randomization whether or not a subject will receive pemetrexed maintenance if eligible**.

Subjects categorized as PD-L1 non-expressing (Part 1B) will be randomized and treated with one of the following open-label treatments:

- **Arm D**: 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, for up to 2 years. Treatment beyond initial investigator-assessed RECIST 1.1 defined progression is permitted if the subject has investigator assessed clinical benefit and is tolerating nivolumab, as specified in Section 4.5.7.
- **Arm F**: Platinum-doublet chemotherapy administered in 3-week cycles for up to a maximum of 4 cycles of IV chemotherapy. Chemotherapy treatment will continue until disease progression, unacceptable toxicity or completion of the 4 cycles, whichever comes first. Choice of chemotherapy regimens is dependent on NSCLC histology.
  Squamous cell:
  Gemcitabine (1000 or 1250 mg/m^2) with cisplatin (75 mg/m^2). Gemcitabine is administered on Day 1 and Day 8 of each cycle; or
  Gemcitabine (1000 mg/m^2) with carboplatin (AUC 5). Gemcitabine is administered on Day 1 and Day 8 of each cycle.
  Non-squamous cell:
  Pemetrexed (500 mg/m^2) with cisplatin (75 mg/m^2) administered on Day 1 of each cycle; or

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

Note: Subjects with non-squamous histology who have stable disease or response after 4 cycles are permitted to continue pemetrexed alone as maintenance therapy until disease progression or unacceptable toxicity. **The investigator must decide prior to randomization whether or not a subject will receive pemetrexed maintenance if eligible**.

- **Arm G**: Nivolumab combined with platinum-doublet chemotherapy administered every 3 weeks. Combination treatment will continue until disease progression, unacceptable toxicity or completion of the 4 cycles, whichever comes first. Choice of platinum-doublet regimens is dependent on NSCLC histology:
  Squamous cell:
  Nivolumab 360 mg administered IV over 30 minutes, followed by gemcitabine (1000 or 1250 mg/m^2) with cisplatin (75 mg/m^2). Gemcitabine is administered on Day 1 and Day 8 of each cycle, or
  Nivolumab 360 mg administered IV over 30 minutes, followed by gemcitabine (1000 mg/m^2) with carboplatin (AUC 5). Gemcitabine is administered on Day 1 and Day 8 of each cycle.
  Non-squamous cell:
  Nivolumab 360 mg administered IV over 30 minutes, followed by pemetrexed (500 mg/m^2) with cisplatin (75 mg/m^2) administered on day 1 of each cycle, or
  Nivolumab 360 mg administered IV over 30 minutes, followed by pemetrexed (500 mg/m^2) with carboplatin (AUC 5 or 6) administered on Day 1 of each cycle.

Note: Subjects with squamous and non-squamous histologies who have stable disease or response after cycle 4 will continue nivolumab 360 mg as maintenance therapy every 3 weeks until disease progression or unacceptable toxicity, for up to 2 years.

Subjects with non-squamous histology (arm G) who have stable disease or response after cycle 4 may continue pemetrexed maintenance therapy with nivolumab. **The investigator must decide prior to the subject's randomization whether or not the subject will receive pemetrexed maintenance therapy, provided the subject is eligible for it.** Treatment will continue until disease progression or unacceptable toxicity.

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

Enrollment of Part 1 will end after approximately 1200 subjects with PD-L1 expressing tumors (Part 1A) have been randomized. At this time, approximately 540 subjects with non-expressing tumors (Part 1B) are expected to be randomized.

The study design schematic is presented in Figure 3.1.2-1.

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3.1.2 Part 2 Design

Subjects will be randomized 1:1 into 2 arms and stratified by the PD-L1 expression level (< 1% versus ≥ 1%), histology (squamous vs non-squamous), and gender (male versus female).

Note: Subjects with tumor samples unevaluable for PD-L1 status will be stratified to < 1% group.

Subjects will receive open-label treatment with one of the following:

- **Arm H**: Nivolumab combined with platinum-doublet chemotherapy administered every 3 weeks. Combination treatment will continue until disease progression, unacceptable toxicity or completion of the 4 cycles, whichever comes first. Choice of platinum-doublet regimens is dependent on NSCLC histology:
  Squamous:
  Nivolumab 360 mg administered IV over 30 minutes, followed by paclitaxel (200 mg/m^2) with carboplatin (AUC 6) administered on Day 1 of each cycle every 21 days.
  Non-squamous:
  Nivolumab 360 mg administered IV over 30 minutes, followed by pemetrexed (500 mg/m^2) with cisplatin (75 mg/m^2) administered on day 1 of each cycle, or
  Nivolumab 360 mg administered IV over 30 minutes, followed by pemetrexed (500 mg/m^2) with carboplatin (AUC 5 or 6) administered on Day 1 of each cycle.

Note: Subjects with squamous and non-squamous histologies who have stable disease or response after cycle 4 will continue nivolumab 360 mg as maintenance therapy every 3 weeks until disease progression or unacceptable toxicity, for up to 2 years.
Subjects with non-squamous histology who have stable disease or response after cycle 4 may continue pemetrexed maintenance therapy with nivolumab. **The investigator must decide prior to the subject's randomization whether or not the subject will receive pemetrexed maintenance therapy, provided the subject is eligible for it.** Treatment will continue until disease progression or unacceptable toxicity.

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

- **Arm I**: Platinum-doublet chemotherapy administered in 3-week cycles for up to a maximum of 4 cycles of IV chemotherapy. Chemotherapy treatment will continue until disease progression, unacceptable toxicity or completion of the 4 cycles, whichever comes first. Choice of chemotherapy regimens is dependent on NSCLC histology:
  Squamous:
  Paclitaxel (200 mg/m^2) with carboplatin (AUC 6) administered on Day 1 of each cycle every 21 days.
  Non-squamous:
  Pemetrexed (500 mg/m^2) with cisplatin (75 mg/m^2) administered on Day 1 of each cycle; or
  Pemetrexed (500 mg/m^2) with carboplatin (AUC 5 or 6) administered on Day 1 of each cycle

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Note: Subjects with non-squamous histology who have stable disease or response after 4 cycles are permitted to continue pemetrexed alone as maintenance therapy until disease progression or unacceptable toxicity. **The investigator must decide prior to randomization whether or not a subject will receive pemetrexed maintenance if eligible.**

Enrollment will end after approximately 750 subjects have been randomized.

The primary endpoint for Part 2 is Overall Survival.

The study design schematic is presented in Figure 3.1.2-1and Figure 3.1.2-2

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Figure 3.1.2-1: Study Design Schematic (Part 1)

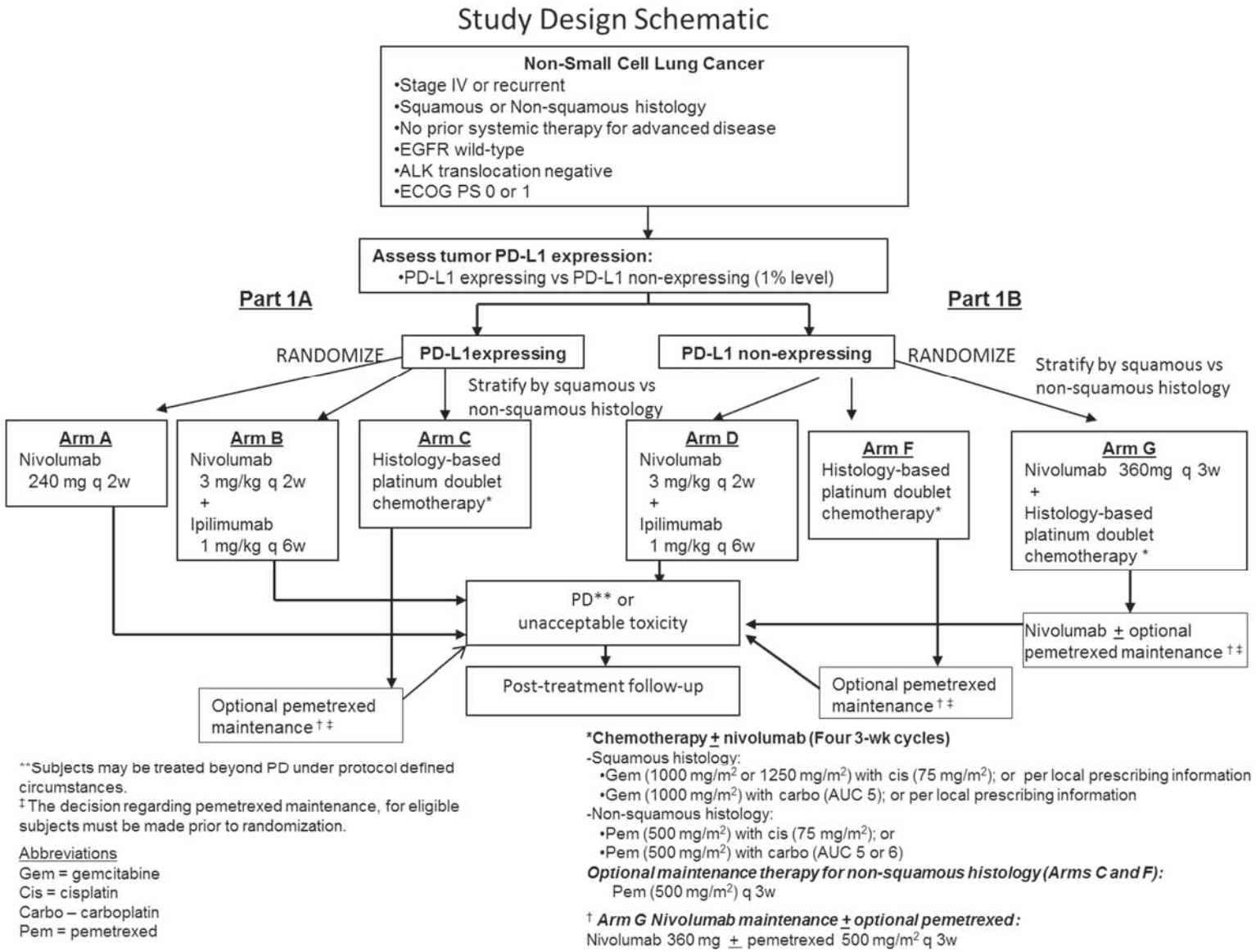

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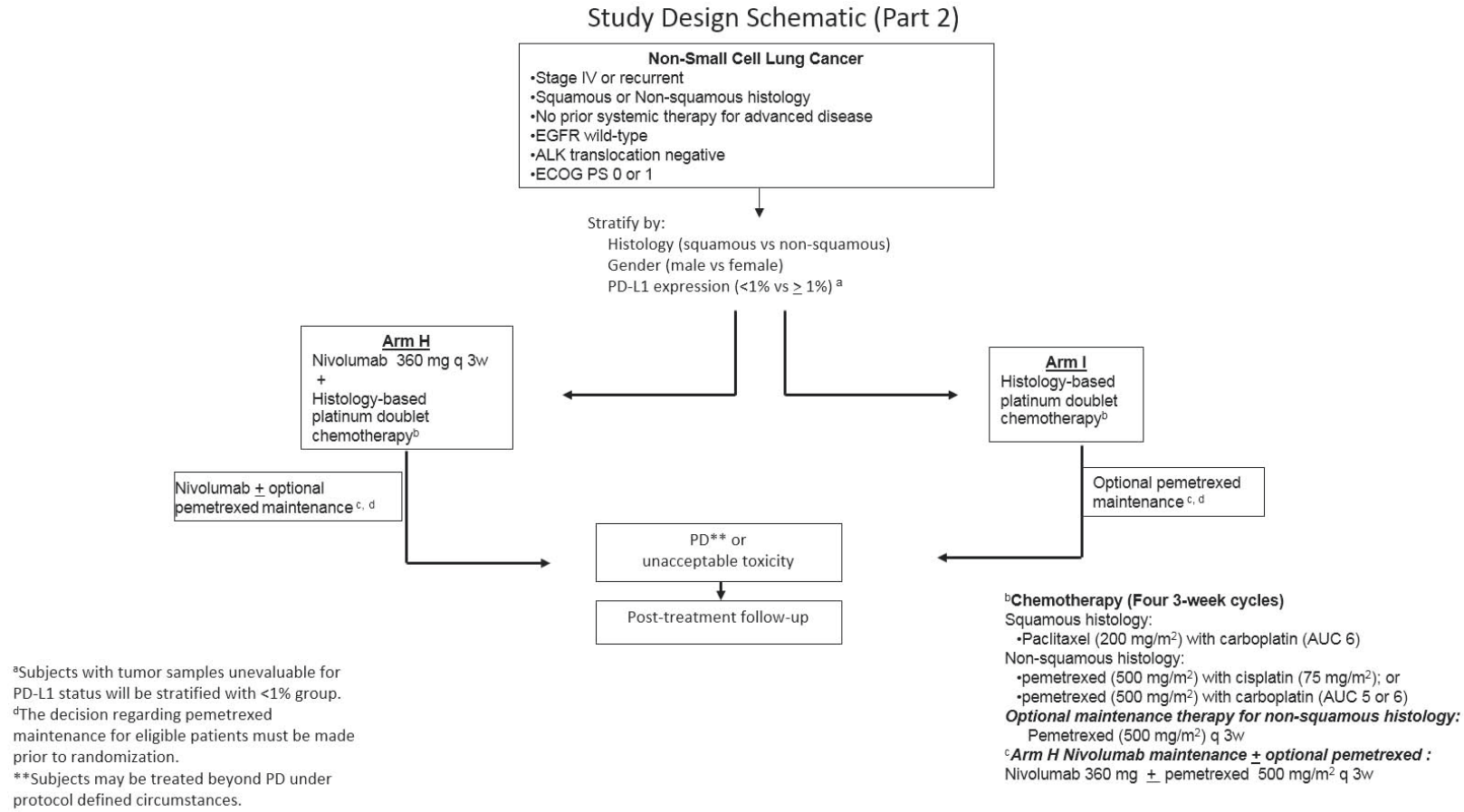
Figure 3.1.2-2: Study Design Schematic (Part 2)



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3.1.3 Screening Phase

- Begins by establishing the subject's initial eligibility and signing of the informed consent (ICF).
- Subject is enrolled using the Interactive Voice Response System (IVRS).
- Tumor tissue (archival or recent tumor biopsy) must be submitted by the site to a third-party vendor for determination of PD-L1 status. Sites will be notified only that there is or is not sufficient tissue for analysis. An email communication will be sent to site for evaluable tumor tissue for PD-L1 expression status determination.

For Part 1 and Part 2, subjects are assessed for study eligibility as described in Table 5.1-1. There is no maximum duration for the screening period. However, if screening extends over a prolonged period, baseline procedures, such as tumor assessments and labs, may need to be repeated so that they fall within the acceptable protocol-specified window. Enrollment for Part 2 will be open after the completion of enrollment and randomization of Part 1.

Note: Those subjects who are enrolled on the last day of enrollment for Part 1 will have only 28 days to complete all the screening assessments and procedures required for randomization. This is to allow the IVRS to transition from Part 1 to Part 2.

3.1.4 Treatment Phase

The treatment phase begins when the randomization call is made into the IVRS. The subject is randomly assigned to one of the six treatment arms. **Study treatment must begin within 3 working days of randomization**. However, for subjects with non-squamous histology randomized to chemotherapy containing arms (arms C, F, G, H and I), study treatment may begin up to 7 calendar days following randomization to allow for pre-medication treatment time.

Treatment with nivolumab or nivolumab with ipilimumab (arms A, B, D, G and H) will be given for up to 24 months in the absence of disease progression or inacceptable toxicity. Chemotherapy (arms C, F and I) will be given as per the study dosing schedule.

3.1.4.1 Part 1

Nivolumab Monotherapy (Arm A)

- Nivolumab 240 mg IV is administered on day 1 of every 2 week cycle until disease progression, discontinuation due to unacceptable toxicity (Section 4.5.6.1), withdrawal of consent or study closure, for up to 2 years.
- Treatment beyond initial investigator-assessed RECIST 1.1-defined progression is permitted if the subject has investigator-assessed clinical benefit and is tolerating treatment, as specified in Section 4.5.7.

Study assessments are to be collected as outlined in Table 5.1-2.

Upon completion of dosing, subjects will enter the Follow-up Phase Table 5.1-6.

Nivolumab plus ipilimumab (Arms B and D)

- Nivolumab 3 mg/kg IV will be administered every 2 weeks.

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- 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, 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, for up to 2 years. Subjects may discontinue only ipilimumab and continue treatment with nivolumab if certain circumstances are met (Sections 4.5.3.2, 4.5.6.1, and 4.5.6.2).
- Treatment beyond initial investigator-assessed RECIST 1.1-defined progression is permitted if the subject has investigator-assessed clinical benefit and is tolerating treatment, as specified in Section 4.5.7.

Study assessments are to be collected as outlined in Table 5.1-4

- Upon completion of dosing, subjects will enter the Follow-up Phase Table 5.1-6.

Platinum Doublet Chemotherapy and Optional Continuation Maintenance (Arms C and F)

- Platinum-doublet chemotherapy is administered IV in 3-week cycles for up to a maximum of 4 cycles of IV chemotherapy
- Platinum-doublet chemotherapy regimen is dependent on NSCLC histology. Subjects with mixed histology should be classified according to the predominant histology:
  Squamous:
  Gemcitabine (1000 or 1250 mg/m^2) with cisplatin (75 mg/m^2). Gemcitabine administered Day 1 and Day 8 of each cycle; or
  Gemcitabine (1000 mg/m^2) with carboplatin (AUC 5). Gemcitabine administered Day 1 and Day 8 of each cycle
  Non-squamous
  Pemetrexed (500 mg/m^2) with cisplatin (75 mg/m^2) administered on Day 1 of each cycle; or
  Pemetrexed (500 mg/m^2) with carboplatin (AUC 5 or 6) administered on Day 1 of each cycle.
- Platinum-doublet chemotherapy will continue until disease progression, unacceptable toxicity (Section 4.5.6.3), or completion of the 4 cycles, whichever comes first.
- **Optional Continuation Maintenance**: Subjects with non-squamous histology who have permitted to continue pemetrexed alone as maintenance therapy until disease progression or unacceptable toxicity. **The investigator must decide prior to the subject's randomization whether or not the subject will receive pemetrexed maintenance therapy, provided the subject is eligible for it**.
  Study assessments are to be collected as outlined in Table 5.1-5
- Upon completion of chemotherapy, subjects will enter Follow-up Phase Table 5.1-6.

Nivolumab plus Platinum-doublet Chemotherapy (Arm G)

- Nivolumab will be administered IV every 3 weeks with platinum-doublet chemotherapy IV for a maximum of 4 cycles of nivolumab/chemotherapy.

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- On the day of infusion, nivolumab is to be administered first. Infusion of the platinum-doublet will start at least 30 minutes after completion of the nivolumab infusion.
- Platinum-doublet chemotherapy regimen is dependent on NSCLC histology. Subjects with mixed histology should be classified according to the predominant histology:
  Squamous:
  Nivolumab 360 mg, followed by gemcitabine (1000 or 1250 mg/m^2) with cisplatin (75 mg/m^2). Gemcitabine administered Day 1 and Day 8 of each cycle; or
  Nivolumab 360 mg, followed by gemcitabine (1000 mg/m^2) with carboplatin (AUC 5). Gemcitabine administered Day 1 and Day 8 of each cycle;
  Non-squamous:
  Nivolumab 360 mg, followed by pemetrexed (500 mg/m^2) with cisplatin (75 mg/m^2) administered on Day 1 of each cycle; or
  Nivolumab 360 mg, followed by pemetrexed (500 mg/m^2) with carboplatin (AUC 5 or 6) administered on Day 1 of each cycle

Following completion of nivolumab/chemotherapy (maximum of 4 cycles), all subjects who have not experienced disease progression will receive nivolumab 360 mg every 3 weeks until the progression of disease, discontinuation due to toxicity, withdrawal of consent, or study closure, for up to 2 years. Subjects with non-squamous histology, in whom the investigator had indicated would receive pemetrexed maintenance if eligible, will receive nivolumab 360 mg with pemetrexed 500 mg/m^2 every 3 weeks until the progression of disease, discontinuation due to toxicity, withdrawal of consent, or study closure.

Treatment with nivolumab beyond initial investigator-assessed RECIST 1.1-defined progression is permitted if the subject has investigator-assessed clinical benefit and is tolerating treatment, as specified in Section 4.5.7.

- Study assessments are to be collected as outlined in Table 5.1-5.
- Upon completion of dosing, subjects will enter Follow-up Phase Table 5.1-6.

3.1.4.2 Part 2

Nivolumab plus Platinum-doublet Chemotherapy (Arm H)

- Nivolumab will be administered IV every 3 weeks with platinum-doublet chemotherapy IV for a maximum of 4 cycles of nivolumab/chemotherapy
- On the day of infusion, nivolumab is to be administered first. Infusion of the platinum-doublet will start at least 30 minutes after completion of the nivolumab infusion.
- Platinum-doublet chemotherapy regimen is dependent on NSCLC histology. Subjects with mixed histology should be classified according to the predominant histology:
  Squamous
  Nivolumab 360 mg administered IV over 30 minutes, followed by paclitaxel (200 mg/m^2) with carboplatin (AUC 6) administered on Day 1 of each cycle every 21 days.

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

Following completion of nivolumab/chemotherapy (maximum of 4 cycles), subjects who have not experienced disease progression will receive nivolumab monotherapy 360 mg every 3 weeks until the progression of disease, discontinuation due to toxicity, withdrawal of consent, or study closure, for up to 2 years. Subjects with non-squamous histology in whom the investigator had indicated would receive pemetrexed maintenance, if eligible will receive nivolumab 360 mg with pemetrexed 500 mg/m^2 every 3 weeks until the progression of disease, discontinuation due to toxicity, withdrawal of consent, or study closure.

Treatment with nivolumab beyond initial investigator-assessed RECIST 1.1-defined progression is permitted if the subject has investigator-assessed clinical benefit and is tolerating treatment, as specified in Section 4.5.7.

- Study assessments are to be collected as outlined in Table 5.1-7.
- Upon completion of dosing, subjects will enter Follow-up Phase (Table 5.1-6).

Platinum Doublet Chemotherapy and Optional Continuation Maintenance (Arm I)

- Platinum-doublet chemotherapy will be administered IV in 3-week cycles for up to a maximum of 4 cycles of IV chemotherapy.
- Platinum-doublet chemotherapy regimen is dependent on NSCLC histology. Subjects with mixed histology should be classified according to the predominant histology:
  Squamous
  Paclitaxel (200 mg/m^2) with carboplatin (AUC 6) administered on Day 1 of each cycle every 21 days.
  Non-squamous
  Pemetrexed (500 mg/m^2) with cisplatin (75 mg/m^2) administered on Day 1 of each cycle; or
  Pemetrexed (500 mg/m^2) with carboplatin (AUC 5 or 6) administered on Day 1 of each cycle
- Platinum-doublet chemotherapy will continue until disease progression, unacceptable toxicity (Section 4.5.6.3) or completion of the 4 cycles, whichever comes first.
- **Optional Continuation Maintenance**: Subjects with non-squamous histology who have stable disease or response after 4 cycles of pemetrexed with cisplatin or carboplatin are permitted to continue pemetrexed alone as maintenance therapy until disease progression or unacceptable toxicity or study closure. **The investigator must decide prior to the subject's randomization whether or not the subject will receive pemetrexed maintenance therapy, provided the subject is eligible for it.**
- Study assessments are to be collected as outlined in Table 5.1-8.
- Upon completion of dosing, subjects will enter Follow-up Phase Table 5.1-6.

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3.1.5 Post-Treatment Follow-up

For subjects in Parts 1 and 2:

- The post-treatment follow-up begins when the decision to discontinue a subject from all treatment is made; this includes optional continuation maintenance therapy.
- 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 5.1-6 until progression is confirmed by the BICR or the start of any subsequent therapy, whichever occurs later.
- 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 randomized 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.
- Study assessments are to be collected as outlined in Table 5.1-6.

3.1.6 Duration of Study

The duration of Part 1A of the study from start of randomization to the final analysis of OS is approximately 34 months. The duration of Part 1B of the study from start of randomization to final analysis of PFS is approximately 23 months. The duration of Part 2 of the study from start of randomization to final analysis of OS is approximately 22 months. Individual sub study (part 1A or part 1B or part 2) will end when analysis of survival is complete.

A DMC will be utilized to provide general oversight and safety considerations for this study, CA209227 (Section 7).

3.2 Post Study Access Therapy

At the conclusion of the study, participants who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study treatment for the maximum treatment duration allowed by the study protocol. Study treatment will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of BMS.

BMS reserves the right to terminate access to study drug if any of the following occur: a) the marketing application is rejected by the responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a government sponsored or private health program; or d) therapeutic alternatives become available in the local market.

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3.3 Study Population

For entry into both Part 1 and Part 2 of 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 ≤ 1.

b) Subjects with histologically confirmed Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer classification (IASLC)[61]) squamous or non-squamous histology, with no prior systemic anticancer therapy (including EGFR and ALK inhibitors) given as primary therapy for advanced or metastatic disease.

Prior adjuvant or neoadjuvant chemotherapy is permitted as long as the last administration of the prior regimen occurred at least 6 months prior to enrollment.

Prior definitive chemoradiation for locally advanced disease is also permitted as long as the last administration of chemotherapy or radiotherapy (which ever was given last) occurred at least 6 months prior to enrollment.

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

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 must have PD -L1 IHC testing, with results, performed by the central lab during the Screening period. (**Note**: Although Part 2 allows subjects with unevaluable samples to randomized, PD-L1 testing must have been performed prior to randomization, and the results must be documented as unevaluable).

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 randomization. The tumor tissue sample may be fresh or archival if obtained within 6 months prior to enrollment, and there can have been no systemic therapy (e.g., adjuvant or neoadjuvant chemotherapy) given after the sample was obtained.

Tissue must be a core needle biopsy, excisional or incisional biopsy. Fine needle biopsies or drainage of pleural effusions with cytospins are not considered adequate for biomarker review and randomization. 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 randomization. Subjects with symptomatic tumor lesions at baseline that may require palliative radiotherapy within 4 weeks of randomization are strongly encouraged to receive palliative radiotherapy prior to randomization.

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 (i.e., subject has not been randomized/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 method(s) of contraception for the duration of treatment with nivolumab and 5 months after the last dose of nivolumab {i.e., 30 days (duration of ovulatory cycle) plus the time required for nivolumab to undergo approximately five half-lives} (for subjects treated in arms A, B, D, G and H).

WOCBP must also agree to follow instructions for method(s) of contraception from the time of enrollment for the duration of treatment with chemotherapy plus 5 half-lives of chemotherapy plus 30 days (duration of ovulatory cycle) for a total of 30 days post treatment completion or a duration specified by the local labels of the chemotherapy drugs received, whichever is longer (for subjects treated in arms C, F and I).

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e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with nivolumab and 7 months after the last dose of nivolumab {i.e., 90 days (duration of sperm turnover) plus the time required for nivolumab to undergo approximately five half-lives} (for subjects treated in arms A, B, D, G and H).

   Males who are sexually active with WOCBP must agree to follow instructions for method(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 post treatment completion or a duration specified by the local labels of the chemotherapy drugs received, whichever is longer (for subjects treated in arms C, F and I).

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

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

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. WOCBP and female partners of male subjects, who are WOCBP, are expected to use one of the highly effective methods of contraception listed below. Male subjects must inform their female partners who are WOCBP of the contraceptive requirements of the protocol and are expected to adhere to using contraception with their partner. Contraception methods are as follows:

1. Progestogen only hormonal contraception associated with inhibition of ovulation.
2. Hormonal methods of contraception including oral contraceptive pills containing combined estrogen + progesterone, vaginal ring, injectables, implants, transdermal and intrauterine hormonal-releasing system (IUS)
3. Intrauterine devices (IUD)
4. Bilateral tubal occlusion
5. Vasectomised partner with documented azoospermia 90 days after procedure

   Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.

- Complete abstinence

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- Complete abstinence is defined as the complete avoidance of heterosexual intercourse (refer to Glossary of Terms)
- Complete abstinence is an acceptable form of contraception for all study drugs and must be used throughout the duration of the study treatment (plus 5 half-lives of the investigational drug plus 30 days).
- It is not necessary to use any other method of contraception when complete abstinence is elected.
- Subjects who choose complete abstinence must continue to have pregnancy tests, as specified in Section 6.4.
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.
- The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

MALE SUBJECTS WITH PARTNERS WHO ARE WOCBP:

Are required to use condoms, in addition to the requirement for their female partners who are WOCBP to use a highly effective method of contraception listed above.

UNACCEPTABLE METHODS OF CONTRACEPTION

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

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; use of an FDA-approved test is strongly encouraged. Subjects with non-squamous histology and 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.

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c) Subjects with untreated CNS metastases are excluded.

d) 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 randomization. In addition, subjects must be either off corticosteroids, or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent) for at least 2 weeks prior to randomization.

e) 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 randomization.

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 randomization 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 randomization. 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).

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.

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 platinum-containing compounds or other study drug components

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5. Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated

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

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria. Subjects not meeting the inclusion/exclusion criteria must not be enrolled into the study. There can be no exceptions to this rule.

3.3.3 Women of Childbearing Potential

A woman of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 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 judgment in checking serum FSH levels. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal:

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

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

3.4 Concomitant Treatments

The following sections apply to both parts 1 and 2 of the study.

3.4.1 Prohibited and/or Restricted Treatments

- The following medications are prohibited during the study (unless utilized to treat a drug related adverse event):
- Immunosuppressive agents.
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 3.4.3)
- Any concurrent anti-neoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of NSCLC)

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Caution should be used regarding the use of herbal medications as there may be as yet unknown interactions with nivolumab and/or ipilimumab. Discontinuation of the use of herbal medications prior to study enrollment is encouraged.

Investigators should refer to the local product labeling for the chemotherapy drugs selected for use in Arms C, F, G, H and I subjects for additional prohibited and restricted concomitant medications.

3.4.2 Other Restrictions and Precautions

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

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

3.4.3 Permitted Therapy

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

For subjects in Arms A, B, D, G, or H regular concomitant use of bisphosphonates and RANK-L inhibitors for prevention or reduction of skeletal-related events in patients with bone metastases is allowed if initiated prior to first dose of study therapy. These agents are prohibited after the start of dosing because preclinical data suggests that they can have immunomodulatory effects, and this can confound the pre-treatment vs post-treatment biomarker analyses if they are started after first dose.

Prior palliative radiotherapy must have been completed at least 2 weeks prior to randomization.

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3.4.3.1 Palliative Local Therapy

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

Subjects requiring palliative local therapy should be evaluated for objective evidence of disease progression prior to the initiation of such therapy, particularly if the most recent tumor assessment was more than 4 weeks prior to the start of local therapy. If progression per RECIST 1.1 is identified on any tumor assessments prior to the initiation of palliative local therapy, then subjects in Arms A, B, D, G, or H must either discontinue study drug treatment or they must meet criteria to continue treatment beyond progression (Section 4.5.7) in order to resume immunotherapy after palliative local therapy. Subjects in Arm C or F who are found to have progression per RECIST 1.1 on any tumor assessments prior to the initiation of palliative local therapy must discontinue chemotherapy.

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

3.5 Discontinuation of Subjects from Treatment

Subjects, in both parts 1 and 2 of the study, 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*
- Additional protocol specified reasons for discontinuation (See Section 4.5.6).

*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

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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 (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

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

3.6 Post Study Drug Study Follow up

In both parts 1 and 2 of this study, overall survival is a key endpoint. Post study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study drug must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

Follow-Up Visit 1 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 80 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 *randomized* subjects outside of the protocol defined window (Table 5.1-6). 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.

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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 Product (IMP) and Non-investigational Product (Non-IMP) and can consist of the following:

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

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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 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
Cisplatin Concentrate for 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.
Gemcitabine Powder for Solution for Infusion [b]	1000 mg/vial	1000 mg per vial/ Open label	1 vial per carton/Open label	White to off-white plug or powder	Store at 15-30° C
Gemcitabine Concentrate for Solution for Infusion [b]	1000 mg/vial	1000 mg per vial/ Open label	1 vial per carton/Open label	Clear, colorless or light straw-colored solution	Store at 2-8° C
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)
Paclitaxel Solution for Injection[b]	100 mg/vial (6 mg/mL)	16.7 mL per vial Open label	4 vials per carton/Open label	Clear, colorless or slightly yellow viscous solution	Store at 15°-30°. Protect from light.

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

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[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).

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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:

Part 1

- Nivolumab
- Ipilimumab
- Gemcitabine
- Cisplatin
- Carboplatin
- Pemetrexed

- **Part 2**
- Nivolumab
- Cisplatin
- Carboplatin
- Pemetrexed
- Paclitaxel

4.2 Non-investigational Product

For both parts 1 and 2, 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 pre-medications associated with the comparator arms and medications used to treat chemotherapy infusion-related reactions. Also, any medications used to treat nivolumab infusion-related reactions (e.g., steroids). These non-investigational products should be sourced by the investigator sites if available and permitted by local regulations.

4.3 Storage and Dispensing

For both parts 1 and 2, 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

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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 (e.g., required diluents, administration sets).

Infusion-related supplies (e.g., 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 in the 4 nivolumab containing arms. 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

CA209227 (CheckMate 227) is a randomized, open-label study utilizing the marker by treatment interaction design.[62] 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 voice response system (IVRS) to obtain the subject number. Every subject that signs the informed consent form must be assigned a subject number in IVRS. Specific instructions for using IVRS will be provided to the investigational site in a separate document. The investigator or designee will register the subject for enrollment by following the enrollment procedures established by BMS. The following information is required for enrollment:

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

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

- Subject number
- Date of birth

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- Histology (squamous or non-squamous). Subjects with mixed histology should be classified according to the predominant histology. Subjects with adenosquamous histology should be classified as non-squamous histology.
- PD-L1 status
- Will subject be treated with maintenance pemetrexed if eligible?

Part 1

Subjects meeting all eligibility criteria will be separated according to PD-L1 status (expressing versus non-expressing, using < 1% vs ≥ 1% expression levels). They will then be stratified by tumor histology (squamous vs non-squamous). Subjects with PD-L1 expressing tumors will be randomized in a 1:1:1 ratio to one of three treatment arms. Subjects with PD-L1 non-expressing tumors will initially be randomized to arms D and F in a 1:1 ratio, until the amendment version number 9 is approved in all concurrently enrolling sites. After the approval of amendment version number 9 in all the concurrently enrolling sites, subjects with PD-L1 non-expressing tumors will be randomized in a 1:1:1 ratio to arms D, F and G respectively.

Part 2

Subjects meeting all eligibility criteria will be randomized in a 1:1 ratio to treatment Arm H or Arm I. The randomization will be stratified by the following factors:

- PD-L1 status (expressing versus non-expressing, using < 1% vs ≥ 1% expression levels)
- Tumor histology (squamous vs non-squamous)
- Gender (male vs female)

Note: subjects whose PD-L1 status is not evaluable will be classified as PD-L1 < 1%. The total number of patients with unevaluable PD-L1 status should not exceed 10% of total randomized patients for Part 2.

Stratification by gender is based on the observation that gender may be an important prognostic factor for patients with cancer. Many studies have shown that women with cancer have improved survival compared to men[63] Gender may have influenced the results of CheckMate 026.

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

4.5 Selection and Timing of Dose for Each Subject

The dosing schedule is detailed below Table 4.5-1, Table 4.5-2, Table 4.5-3 and Table 4.5-4.

All subjects will be monitored continuously for AEs while on study treatment. Treatment modifications (e.g., dose delay, reduction, retreatment, or discontinuation) will be based on specific laboratory and adverse event criteria, as described in Sections 4.5.3, 4.5.4, 4.5.5, and 4.5.6.

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Table 4.5-1: Dosing Schedule for Part 1*

	Week 1 ± 3 Days	**Week 2**	**Week 3** ± 3 Days	**Week 4**	**Week 5** ± 3 Days	**Week 6**
Arm A: Nivolumab 240mg q 2 weeks[a]	**Day 1** Nivolumab		**Day 1** Nivolumab		**Day 1** Nivolumab	
Arms B and D: 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	
Arms C and F: Platinum doublet chemotherapy: q 3w x 4 followed by optional maintenance Pemetrexed for non-squamous histology	Day 1: Gemcitabine/Cisplatin or Gemcitabine/Carboplatin or Pemetrexed/Cisplatin or Pemetrexed/Carboplatin	Day 8 Gemcitabine		Day 1: Gemcitabine/Cisplatin or Gemcitabine/Carboplatin or Pemetrexed/Cisplatin or Pemetrexed/Carboplatin	Day 8 Gemcitabine	
Arm: G Nivolumab 360 mg + Platinum-doublet chemotherapy q 3w x 4 followed by maintenance nivolumab (360 mg) therapy for subjects without progressive disease	**Day 1** Nivolumab + Gemcitabine/Cisplatin or Gemcitabine/Carboplatin or Pemetrexed/Cisplatin or Pemetrexed/Carboplatin	**Day 8** Gemcitabine		**Day 1** Nivolumab + Gemcitabine/Cisplatin or Gemcitabine/Carboplatin or Pemetrexed/Cisplatin or Pemetrexed/Carboplatin	**Day 8** Gemcitabine	

* Both nivolumab and ipilimumab should be administered as 30 minute infusions (Section 1.1.5). For arms B, D and G, nivolumab is to be administered first. The second infusion will be ipilimumab (arms B and D) or platinum-doublet chemotherapy (arm G), and will start at least 30 minutes after completion of the nivolumab infusion.

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[a] continues until disease progression, discontinuation due to unacceptable toxicity, withdrawal of consent, or study closure, for up to two years.

Table 4.5-2: Maintenance Schedule for Optional Pemetrexed[a] (Arms C and F) and Nivolumab + Pemetrexed (Arm G) for Subjects with non-Squamous Histology for Part 1

	Week 1 ± 3 Days	**Week 2**	**Week 3** ± 3 Days	**Week 4** ± 3 Days	**Week 5** ± 3 Days	**Week 6**
Arm C and F: Pemetrexed 500 mg/m^2	**Day 1** Pemetrexed			**Day 1** Pemetrexed		
Arm G: Nivolumab 360 mg + Pemetrexed 500 mg/m2	Day 1 Nivolumab + Pemetrexed			Day 1 Nivolumab + Pemetrexed		

[a] The investigator must decide prior to the subject's randomization whether or not the subject will receive pemetrexed maintenance therapy, provide the subject is eligible for it.

Maintenance therapy with nivolumab continues until disease progression, discontinuation due to unacceptable toxicity, withdrawal of consent, or study closure, for up to two years. Maintenance therapy with pemetrexed continues until disease progression, discontinuation due to unacceptable toxicity, withdrawal of consent, or study closure.

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Table 4.5-3: Dosing Schedule for Part 2*

	Week 1 ± 3 Days	**Week 4 ± 3 Days**
Arm: H Nivolumab 360 mg + Platinum-doublet chemotherapy q 3w x 4 followed by maintenance nivolumab (360 mg) therapy for subjects without progressive disease	Day 1 Nivolumab + Paclitaxel/Carboplatin or Pemetrexed/Cisplatin or Pemetrexed/Carboplatin	Day 1 Nivolumab + Paclitaxel/Carboplatin or Pemetrexed/Cisplatin or Pemetrexed/Carboplatin
Arm I: Platinum doublet chemotherapy: q 3w x 4 followed by optional maintenance Pemetrexed for non-squamous histology	Day 1: Paclitaxel/Carboplatin or Pemetrexed/Cisplatin or Pemetrexed/Carboplatin	Day 1: Paclitaxel/Carboplatin or Pemetrexed/Cisplatin or Pemetrexed/Carboplatin

* Nivolumab should be administered as 30 minute infusions (Section 1.1.5). For arm H, nivolumab is to be administered first. The second infusion will be platinum-doublet chemotherapy, and will start at least 30 minutes after completion of the nivolumab infusion.

Table 4.5-4: Maintenance Schedule for Optional Pemetrexed[a] (Arm I) and Nivolumab + Pemetrexed (Arm H) for Subjects with non-Squamous Histology for Part 2

	Week 1 ± 3 Days	**Week 4 ± 3 Days**
Arm I: Pemetrexed 500 mg/m^2	Day 1 Pemetrexed	Day 1 Pemetrexed
Arm H:	Day 1	Day 1

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Table 4.5-4: Maintenance Schedule for Optional Pemetrexed[a] (Arm I) and Nivolumab + Pemetrexed (Arm H) for Subjects with non-Squamous Histology for Part 2

	Week 1 ± 3 Days	**Week 4 ± 3 Days**
Nivolumab 360 mg + Pemetrexed 500 mg/m^2	Nivolumab + Pemetrexed	Nivolumab + Pemetrexed

[a] The investigator must decide prior to the subject's randomization whether or not the subject will receive pemetrexed maintenance therapy, provide the subject is eligible for it.

Maintenance therapy with nivolumab continues until disease progression, discontinuation due to unacceptable toxicity, withdrawal of consent, or study closure, for up to two years. Maintenance therapy with pemetrexed continues until disease progression, discontinuation due to unacceptable toxicity, withdrawal of consent, or study closure.

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4.5.1 Part 1

4.5.1.1 Arm A Dosing (Nivolumab monotherapy)

Subjects randomized to Arm A will receive treatment with nivolumab at a dose of 240 mg as a 30-minute IV infusion, on Day 1 of every 2 week treatment cycle, for up to 2 years, until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.

There will be no dose escalations or reductions of nivolumab allowed. Subjects may be dosed no less than 12 days from the previous dose. There are no premedications recommended for nivolumab on the first cycle.

Subjects should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, subjects should be managed according to Section 4.5.9.

Doses of nivolumab may be delayed or discontinued depending on how well the subject tolerates the treatment. See Sections 4.5.3.1, 4.5.5.1, or 4.5.6.1 for more details regarding dose delays, retreatment, and discontinuations.

4.5.1.2 Arms B and D Dosing (Nivolumab plus Ipilimumab)

Subjects randomized to Arms B and D 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, for up to 2 years, until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.

When nivolumab and ipilimumab 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 second infusion will always be ipilimumab and will start no sooner than 30 minutes after completion of the nivolumab infusion. Subjects who require small volumes may infuse over < 30 minutes but no less than 20 minutes.

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 assessed as per Table 5.1-4. 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. Use baseline weight at cycle 1 and prior dose weight at cycle 2 and onwards to calculate weight difference. 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 4.5.9.

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Doses of nivolumab and/or ipilimumab may be interrupted, delayed, or discontinued depending on how well the subject tolerates the treatment. For more details, see sections 4.5.3.2 (dose delays), 4.5.5.1, 4.5.5.2 (resuming treatment), and 4.5.6.1, 4.5.6.2 (discontinuations).

4.5.1.3 Arms C and F Dosing (Platinum Doublet Chemotherapy)

Squamous Histology Chemotherapy Options

Subjects with squamous histology who are randomized to Arms C or F may receive either of the following gemcitabine/platinum regimens:

Gemcitabine/Cisplatin

Subjects will receive gemcitabine at a dose of 1000 or 1250 mg/m^2 for a 30-minute IV infusion on days 1 and 8 with cisplatin at a dose of 75 mg/m^2 as a 30 to 120-minute IV infusion on Day 1 of a 3-week treatment cycle for up to 4 cycles.

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 patients following the end of the gemcitabine infusion. Pretreatment hydration for cisplatin can follow local standard of care, or 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.

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

Doses of gemcitabine and/or cisplatin may be interrupted, delayed, reduced, or discontinued depending on how well the subject tolerates the treatment. See the following sections for more details: 4.5.3.3 (dose delays); 4.5.4.2, 4.5.4.3, and 4.5.4.4 (dose reductions); 4.5.5.3 (retreatment), and 4.5.6.3 (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 gemcitabine/carboplatin for the remainder of the platinum doublet cycles (up to 4 cycles in total). Dosing for gemcitabine/carboplatin for such subjects should follow the instructions in the Gemcitabine/Carboplatin section below.

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Gemcitabine/Carboplatin

Subjects will receive gemcitabine at a dose of 1000 mg/m^2 as a 30-minute IV infusion on Days 1 and 8 with carboplatin at a dose of AUC 5 as a 30-minute IV infusion, on Day 1 of a 3-week cycle, for up to 4 cycles, or at doses per the local prescribing information.

Gemcitabine 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.

Carboplatin should be given following gemcitabine on Day 1 of each cycle, and the carboplatin dose will be calculated using the Calvert formula as follows:

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

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

Doses of gemcitabine and/or carboplatin may be interrupted, delayed, reduced, or discontinued depending on how well the subject tolerates the treatment. See the following sections for more details: 4.5.3.3 (dose delays); 4.5.4.2, 4.5.4.3, and 4.5.4.4, and (dose reductions); 4.5.5.3 (retreatment), and 4.5.6.3 (dose discontinuations).

Non-Squamous Histology Chemotherapy Options

Subjects with non-squamous histology who are randomized to Arms C, F may receive one of the following pemetrexed/platinum regimens, with or without pemetrexed continuation maintenance therapy:

Pemetrexed/Cisplatin With or Without Pemetrexed Continuation Maintenance

Subjects will receive pemetrexed at a dose of 500 mg/m^2 as a 10-minute IV infusion on Day 1 with cisplatin at a dose of 75 mg/m² as a 120-minute IV infusion on Day 1 of a 3-week treatment cycle, for up to 4 cycles. (Note: calculated CrCl must be ≥ 45 ml/min for pemetrexed to be dosed.)

After cycle 4, subjects with stable disease or response may also discontinue cisplatin and continue pemetrexed at the same dose and schedule as continuation maintenance until progression, unacceptable toxicity, or withdrawal of consent. In subjects who required pemetrexed dose reduction due to toxicity during the pemetrexed/cisplatin combination cycles, the dose of pemetrexed may be escalated to 500 mg/m^2 after the discontinuation of cisplatin, at the

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investigator's discretion and according to local standards, if the prior toxicity was felt to be related mainly to cisplatin.

Note: Investigators must indicate, at the time of randomization, whether or not a subject will be treated with pemetrexed continuation maintenance if eligible to do so. If the investigator subsequently decides that a subject should not be treated with pemetrexed continuation maintenance, even though eligible, or decides to treat a subject for whom the investigator had indicated at randomization that maintenance would not be used, this decision must be discussed with the medical monitor.

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.

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

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

Doses of pemetrexed and/or cisplatin may be interrupted, delayed, reduced, or discontinued depending on how well the subject tolerates the treatment See the following sections for more details: 4.5.3.3 (dose delays); 4.5.4.2, 4.5.4.3, and 4.5.4.4 (dose reductions); 4.5.5.3 (retreatment), and 4.5.6.3 (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.

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Subjects who discontinue cisplatin alone may, at the investigator's discretion, be switched to pemetrexed/carboplatin for the remainder of the platinum doublet cycles (up to 4 cycles in total). Dosing for pemetrexed/carboplatin for such subjects should follow the instructions in the Pemetrexed/Carboplatin with or without Pemetrexed Continuation Maintenance section below.

Pemetrexed/Carboplatin With or Without Pemetrexed Continuation Maintenance

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

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

Note: Investigators must indicate, at the time of randomization, whether or not a subject will be treated with pemetrexed continuation maintenance if eligible to do so. If the investigator subsequently decides that a subject should not be treated with pemetrexed continuation maintenance, even though eligible, or decides to treat a subject for whom the investigator had indicated at randomization that maintenance would not be used, this decision must be discussed with the medical monitor.

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.

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

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

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

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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 randomization in anticipation of pemetrexed should they be randomized to Arm C, F, G, H or I.)

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

Doses of pemetrexed and/or carboplatin may be interrupted, delayed, reduced, or discontinued depending on how well the subject tolerates the treatment. See Sections 4.5.3.3, 4.5.4.2, 4.5.4.3, 4.5.4.4, 4.5.5.3, and 4.5.6.3 for more details regarding dose delays, reductions, retreatment, and discontinuations.

4.5.1.4 Arm G Dosing (Nivolumab plus platinum-doublet chemotherapy)

Squamous Histology Chemotherapy Options

Subjects with squamous histology who are randomized to Arm G may receive either of the following nivolumab plus gemcitabine/platinum regimens:

Nivolumab plus Gemcitabine/Cisplatin

Subjects will receive nivolumab at a dose of 360 mg as 30 minute IV infusion on day 1, followed by gemcitabine at a dose of 1000 or 1250 mg/m^2 for a 30 minute IV infusion with cisplatin at a dose of 75 mg/m^2 as a 30 to 120-minute IV infusion, of a 3-week treatment cycle for up to 4 cycles. Gemcitabine will also be administered at a dose of 1000 or 1250 mg/m^2 for a 30 minute IV infusion on day 8 of each 3-week treatment cycle.

At the time of discontinuation of gemcitabine/cisplatin, subjects who have not experienced disease progression will continue to receive nivolumab at a dose of 360 mg as 30 minute IV infusion on day 1 of a 3-week treatment cycle. Treatment will continue, for up to 2 years, until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.

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 patients following the end of the gemcitabine infusion. Pretreatment hydration for cisplatin can follow local standard of care, or 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.

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

Doses of gemcitabine and/or cisplatin may be interrupted, delayed, reduced, or discontinued depending on how well the subject tolerates the treatment. See the following sections for more details: 4.5.3.4 (dose delays): 4.5.4.2, 4.5.4.3, and 4.5.4.4 (dose reductions); 4.5.5.4 (retreatment), and 4.5.6.3 (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 gemcitabine/carboplatin for the remainder of the platinum doublet cycles (up to 4 cycles in total). Dosing for gemcitabine/carboplatin for such subjects should follow the instructions in the Nivolumab plus Gemcitabine/Carboplatin section below.

Nivolumab plus Gemcitabine/Carboplatin

Subjects will receive nivolumab at a dose of 360 mg as 30 minute IV infusion on day 1, followed by gemcitabine at a dose of 1000 mg/m^2 as a 30-minute IV infusion with carboplatin at a dose of AUC 5 as a 30-minute IV infusion, of a 3-week treatment cycle for up to 4 cycles. Gemcitabine will also be administered at a dose of 1000 mg/m^2 as a 30 minute IV infusion on day 8 of each 3-week treatment cycle.

At the time of discontinuation of gemcitabine/carboplatin, subjects who have not experienced disease progression will continue to receive nivolumab at a dose of 360 mg as 30 minute IV infusion on day 1 of a 3-week treatment cycle. Treatment will continue, for up to 2 years, until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.

Gemcitabine 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.

Carboplatin should be given following gemcitabine on Day 1 of each cycle, and the carboplatin dose will be calculated using the Calvert formula as follows:

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

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

Doses of gemcitabine and/or carboplatin may be interrupted, delayed, reduced, or discontinued depending on how well the subject tolerates the treatment. See the following sections for more details: 4.5.3.4 (dose delays): 4.5.4.2, 4.5.4.3, and 4.5.4.4 (dose reductions); 4.5.5.4 (retreatment), and 4.5.6.3 (dose discontinuations).

Nivolumab maintenance therapy

Subjects who have not experienced disease progression after 4 cycles of nivolumab/chemotherapy will receive nivolumab maintenance therapy at a dose of 360 mg as 30 minute IV infusion on day 1 of a 3-week treatment cycle. Treatment will continue, for up to 2 years, until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.

Non-squamous Histology Chemotherapy Options

Nivolumab plus Pemetrexed/Cisplatin

Subjects will receive nivolumab at a dose of 360 mg as 30 minute IV infusion on day 1, followed by pemetrexed at a dose of 500 mg/m^2 as a 10-minute IV infusion with cisplatin at a dose of 75 mg/m² as a 120-minute IV infusion, of a 3-week treatment cycle, for up to 4 cycles. . (Note: calculated CrCl must be ≥ 45 mg/min for pemetrexed to be dosed).

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

***Note: Investigators must indicate, at the time of randomization, whether or not a subject will be treated with pemetrexed continuation maintenance if eligible to do so. If the investigator subsequently decides that a subject should not be treated with pemetrexed continuation maintenance, even though eligible, or decides to treat a subject for whom the investigator had indicated at randomization that maintenance would not be used, this decision must be discussed with the medical monitor.**

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.

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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.

Premedications for use with pemetrexed: Oral corticosteroid should be given according to local standards at a dose equivalent to dexamethasone 4 mg BID on the day prior to, the day of, and the day after the administration of pemetrexed. Dexamethasone is allowed as premedication in arm G during the 4 cycles of platinum-based chemotherapy. 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 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 randomization in anticipation of pemetrexed should they be randomized to Arm C, F, G, H or I).

Premedications for use with pemetrexed/cisplatin: Antiemetic premedication will be administered according to local standards. Recommended antiemetic treatments are dexamethasone (dosing according to local standards; an equivalent dose of another corticosteroid may be substituted) and a 5-HT3 receptor antagonist (type per investigator discretion and local standards-of-care). Dexamethasone is allowed as premedication in arm G during the 4 cycles of platinum-based chemotherapy. Additional use of antiemetic premedications may be employed at the discretion of the Investigator.

Doses of pemetrexed and/or cisplatin may be interrupted, delayed, reduced, or discontinued depending on how well the subject tolerates the treatment See the following sections for more details: 4.5.3.4 (dose delays), 4.5.4.2, 4.5.4.3, and 4.5.4.4 (dose reductions), 4.5.5.4 (retreatment), and 4.5.6.3 (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 (up to 4 cycles in total). Dosing for pemetrexed/carboplatin for such subjects should follow the instructions in the Pemetrexed/Carboplatin with or without Pemetrexed Continuation Maintenance section below.

Nivolumab plus Pemetrexed/Carboplatin

Subjects will receive nivolumab at a dose of 360 mg as 30 minute IV infusion on day 1, followed by pemetrexed at a dose of 500 mg/m^2 as a 10-minute IV infusion with carboplatin at a dose of

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AUC 5 or 6 as a 30-minute IV infusion, on Day 1 of a 3-week treatment cycle, for up to 4 cycles. (Note: calculated CrCl must be ≥ 45 ml/min for pemetrexed to be dosed).

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

***Note: Investigators must indicate, at the time of randomization, whether or not a subject will be treated with pemetrexed continuation maintenance if eligible to do so. If the investigator subsequently decides that a subject should not be treated with pemetrexed continuation maintenance, even though eligible, or decides to treat a subject for whom the investigator had indicated at randomization that maintenance would not be used, this decision must be discussed with the medical monitor.**

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.

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

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

Premedication for use with pemetrexed: Oral corticosteroid should be given according to local standards at a dose equivalent to dexamethasone 4 mg BID on the day prior to, the day of, and the day after the administration of pemetrexed. Dexamethasone is allowed as premedication in arm G during the 4 cycles of platinum-based chemotherapy. 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 randomization in anticipation of pemetrexed should they be randomized to Arm C, F, G, H or I).

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Premedications for use with pemetrexed/carboplatin: Antiemetic premedication will be administered according to local standards. Recommended antiemetic treatments are dexamethasone (dosing according to local standards; an equivalent dose of another corticosteroid may be substituted) and a 5-HT3 receptor antagonist (type per investigator discretion and local standards-of-care). Dexamethasone is allowed as premedication in arm G during the 4 cycles of platinum-based chemotherapy. Additional use of antiemetic premedications may be employed at the discretion of the Investigator.

Doses of pemetrexed and/or carboplatin may be interrupted, delayed, reduced, or discontinued depending on how well the subject tolerates the treatment. See Sections 4.5.3.4, 4.5.4.3, 4.5.4.4 4.5.5.4, and 4.5.6.3 for more details regarding dose delays, reductions, retreatment, and discontinuations.

4.5.2 Part 2

4.5.2.1 Arm H Dosing (Nivolumab plus platinum-doublet chemotherapy)

Squamous Histology Chemotherapy

Nivolumab plus Paclitaxel/Carboplatin

Subjects will receive nivolumab at a dose of 360 mg as 30 minute IV infusion on day 1, followed by paclitaxel at a dose of 200 mg/m^2 as a 180-minute IV infusion, with carboplatin at a dose of AUC 6 as a 30 to 60-minute IV infusion, both on Day 1 of a treatment cycle every 3 weeks for 4 cycles.

At the time of discontinuation of paclitaxel/carboplatin, subjects who have not experienced disease progression will continue to receive nivolumab at a dose of 360 mg as 30 minute IV infusion on day 1 of a 3-week treatment cycle. Treatment will continue, for up to 2 years, until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.

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.

Carboplatin should be given following paclitaxel on Day 1 of each cycle, and the carboplatin dose will be calculated using the Calvert formula as follows:

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

Premedications for use for paclitaxel and carboplatin: Oral or IV corticosteroid should be given prior to paclitaxel according to local standard. Such premedication may consist of oral dexamethasone 20 mg 12 hours and 6 hours prior to paclitaxel administration. Oral or IV

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diphenydramine 50 mg (or its equivalent) and an H2-blocker (per local standard of care) should be administered 30 to 60 minutes prior to paclitaxel infusion. Antiemetic premedication will be administered according to local standards. Recommended antiemetic treatments are dexamethasone (dosing according to local standards; an equivalent dose of another corticosteroid may be substituted) and a 5-HT3 receptor antagonist (type per investigator discretion and local standards of care). Additional use of antiemetic premedications may be employed at the discretion of the investigator per local standards of care.

All subjects should be carefully monitored for infusion reactions during the paclitaxel administration. Subjects should be treated in a facility with the necessary medical-resuscitation equipment and medications on hand to manage serious acute infusion reactions.

Doses of paclitaxel and/or carboplatin may be interrupted, delayed, reduced, or discontinued depending on how well the subject tolerates the treatment. See the following sections for more details: 4.5.3.4 (dose delays) 4.5.4.2, 4.5.4.3, 4.5.4.4 (dose reductions), 4.5.5.4 (retreatment), and 4.5.6.3 (dose discontinuations).

Non-squamous Histology Chemotherapy Options

The non-squamous histology chemotherapy dosing for Arm H will be identical to that in Arm G. Subjects may receive either nivolumab plus pemetrexed/cisplatin or nivolumab plus pemetrexed/carboplatin. Please refer to Section 4.5.1.4 for details. Dexamethasone is allowed as premedication for pemetrexed, pemetrexed/carboplatin or pemetrexed/cisplatin in arm H during the 4 cycles of platinum-based chemotherapy.

4.5.2.2 Arm I Dosing (Platinum Doublet Chemotherapy)

Squamous Histology Chemotherapy

Paclitaxel/Carboplatin

Subjects will receive paclitaxel at a dose of 200 mg/m^2 as a 180-minute IV infusion, followed by carboplatin at a dose of AUC 6 as a 30 to 60-minute IV infusion, both on Day 1 of a treatment cycle every 3 weeks for 4 cycles.

Paclitaxel 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 weight used to calculate the previous dose.

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

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

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Premedications: Oral or IV corticosteroid should be given prior to paclitaxel according to local standard. Such premedication may consist of oral dexamethasone 20 mg 12 hours and 6 hours prior to paclitaxel administration. Oral or IV diphenydramine 50 mg (or its equivalent) and an H2-blocker (per local standard of care) should be administered 30 to 60 minutes prior to paclitaxel infusion. Antiemetic premedication will be administered according to local standards. Recommended antiemetic treatments are dexamethasone (dosing according to local standards; an equivalent dose of another corticosteroid may be substituted) and a 5-HT3 receptor antagonist (type per investigator discretion and local standards of care). Additional use of antiemetic premedications may be employed at the discretion of the investigator per local standards of care.

All subjects should be carefully monitored for infusion reactions during the paclitaxel administration. Subjects should be treated in a facility with the necessary medical-resuscitation equipment and medications on hand to manage serious acute infusion reactions.

Doses of paclitaxel and/or carboplatin may be interrupted, delayed, reduced, or discontinued depending on how well the subject tolerates the treatment. See the following sections for more details: 4.5.3.4 (dose delays); 4.5.4.2, 4.5.4.3, and 4.5.4.4 (dose reductions); 4.5.5.3 (retreatment), and 4.5.6.3 (dose discontinuations).

4.5.2.3 Non-Squamous Histology Chemotherapy Options for Arm I, Part 2

Subjects with non-squamous histology who are randomized to Arm I may receive either pemetrexed/cisplatin or pemetrexed/carboplatin regimen, with or without pemetrexed continuation maintenance therapy, which is the same regimen for those assigned to Arms C and F. Please refer to Section 4.5.1.3 for details.

4.5.3 Dose Delay Criteria

Tumor assessments for all subjects in both parts 1 and 2 should continue as per protocol **even if dosing is delayed**.

4.5.3.1 Dose Delay for Arm A (Nivolumab monotherapy, Part 1)

Nivolumab 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.

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- Any AE, laboratory abnormality or inter-current illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Subjects who require delay of nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab dosing when re-treatment criteria are met (per Section 4.5.5.1).

4.5.3.2 Dose Delay for Arms B and D (Nivolumab plus Ipilimumab, Part 1)

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. (Refer to Section 4.5.5.2 for further details.)

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.

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- 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 4.5.6.2.

4.5.3.3 Dose Delay Criteria for Arms C, F, and I (Platinum Doublet Chemotherapy)

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

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

In addition, subjects receiving cisplatin with pemetrexed or gemcitabine must discontinue cisplatin if the calculated creatinine clearance decreases to < 50 mL/min (based on the Cockroft Gault formula). The other drug (pemetrexed or gemcitabine) may be continued, and the platinum agent may, at the investigator's discretion, be switched to carboplatin for the remainder of the platinum doublet cycles (up to 4 cycles in total) when the subject meets retreatment criteria, as specified in Section 4.5.5.3. Note that pemetrexed can only be administered if CrCl is ≥ 45 ml/min (calculated per Cockroft-Gault formula).

Subjects receiving gemcitabine with cisplatin or carboplatin should omit the Day 8 gemcitabine dose for any of the following on Day 8 of any cycle:

- ANC < 1,000/mm^3
- Platelets < 75,000/mm^3

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

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may be omitted for that cycle while the other agent is given. In order to maintain synchronized dosing of the regimen, the omitted agent should be resumed with the next scheduled cycle once the AE has improved and retreatment criteria are met. Please refer to Section 4.5.4.2 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 4.5.5.3).

4.5.3.4 Dose Delay Criteria for Arm G and H (Nivolumab plus Platinum-Doublet Chemotherapy)

In Arms G and H, dosing of all drugs should be delayed if any criteria in sections 4.5.3.1 (Arm A, nivolumab monotherapy) or 4.5.3.3 or 4.5.3.4 (Arms C, F, or G, platinum-doublet chemotherapy) are met. After subjects have completed 4 cycles of platinum-doublet chemotherapy, and are on nivolumab maintenance therapy, dose delay criteria for nivolumab monotherapy should apply. For those subjects continuing with pemetrexed maintenance therapy, dose delay criteria for platinum-doublet chemotherapy should apply for pemetrexed delay.

4.5.4 Dose Reductions

4.5.4.1 Reductions for Nivolumab or Ipilimumab

There will be no dose reductions for nivolumab or ipilimumab.

4.5.4.2 Dose Reductions for Platinum Doublet Chemotherapy (Arms C, F, G, H and I)

Dose reductions of platinum doublet chemotherapy may be required, and will be performed according to Table 4.5.4.2-1 or per institutional guidelines. The dosing reduction criteria will apply to Arms C, F, G, H and I. 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 4.5.4.2-1: Dose Modifications of Chemotherapeutic Agents

Dose Level	Gemcitabine	Pemetrexed	Cisplatin	Carboplatin	Carboplatin	Paclitaxel
Starting dose	1000 or 1250 mg/m² (with cisplatin) or 1000 mg/m² (with carboplatin)	500 mg/m²	75 mg/m²	AUC 5 or 6 with pemetrexed/ or AUC 5 with gemcitabine	AUC 6 with paclitaxel	200 mg/m^2
First dose reduction	750 or 950 mg/m² (with cisplatin) or 750 mg/m²	375 mg/m²	56 mg/m²	AUC 4 or 5 with pemetrexed or AUC 4	AUC 5 with paclitaxel	150 mg/m^2

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Table 4.5.4.2-1: Dose Modifications of Chemotherapeutic Agents

Dose Level	Gemcitabine	Pemetrexed	Cisplatin	Carboplatin	Carboplatin	Paclitaxel
	(with carboplatin			with gemcitabine		
Second dose reduction	500 or 625 mg/m² (with cisplatin) or 500 mg/m² (with carboplatin)	250 mg/m²	38 mg/m²	AUC 3 or 4 with pemetrexed or AUC 3 with	AUC 4 with paclitaxel	100 mg/m^2
Third dose reduction	Discontinue	Discontinue	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.

4.5.4.3 Platinum Doublet Chemotherapy - Dose Reductions for Hematologic Toxicity (Arms C, F, G, H and I)

Dose modifications for hematologic toxicities (according to CTCAE version 4) are summarized in Table 4.5.4.3-1. 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 4.5.4.3-1: Dose Modifications for Hematologic Toxicity (Based on Nadir Counts) (Arms C,F,G,H,I)

Toxicity	Gemcitabine	Pemetrexed	Cisplatin	Carboplatin	Paclitaxel
Neutrophils Count Decreased					
Grade 4 (< 500/mm3 or < 0.5 x 109/L)	Reduce one dose level	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/mm3; 25.0 < 50.0 x 109/L)	Reduce one dose level	Reduce one dose level	Reduce one dose level	Reduce one dose level	Reduce one dose level
Grade 4	Reduce one dose level	Reduce one dose level	Reduce one dose level	Reduce one dose level	Reduce one dose level

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Table 4.5.4.3-1: Dose Modifications for Hematologic Toxicity (Based on Nadir Counts) (Arms C,F,G,H,I)

Toxicity	Gemcitabine	Pemetrexed	Cisplatin	Carboplatin	Paclitaxel
(< 25,000/mm3; < 25.0 x 109/L)					

4.5.4.4 Platinum Doublet Chemotherapy - Dose Reductions for Non-Hematologic Toxicities (Arms C, F, G, H and I)

Dose adjustments for platinum doublet chemotherapy for non-hematologic toxicities during treatment are described in Table 4.5.4.4-1. All dose reductions should be made based on the worst grade toxicity. Subjects experiencing any of the toxicities detailed in Table 4.5.4.4-1 during the previous cycle should have their chemotherapy delayed until retreatment criteria are met (per Section 4.5.5.3 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 below.

Table 4.5.4.4-1: Dose Modifications for Non-hematologic Toxicity

Toxicity	Gemcitabine	Pemetrexed	Cisplatin	Carboplatin	Paclitaxel
Febrile Neutropenia Grade ≥ 3	Reduce one dose level	Reduce one dose level	Reduce one dose level	Reduce one dose level	Reduce one dose level
Diarrhea Grade ≥ 3	Reduce one dose level	Reduce one dose level	No change	No change	Reduce one dose level
Allergic reaction[a] Grade ≥ 3	Discontinue	Discontinue	Discontinue	Discontinue	Discontinue
Neuropathy Grade 2	No change	No change	Reduce one dose level	No change	Reduce one dose level
Neuropathy Grade ≥ 3	Discontinue	Discontinue	Discontinue	Discontinue	Discontinue
Calculated creatinine clearance < 50 mL/min	No change	No change	Discontinue	Discontinue if creatinine clearance < 20 ml/min	No change
Other Grade ≥ 3 toxicity (except for fatigue and transient arthralgia and myalgia)	Adjust as medically indicated	Adjust as medically indicated	Adjust as medically indicated	Adjust as medically indicated	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.

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4.5.5 Criteria to Resume Dosing

4.5.5.1 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 4.5.6.1) 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 after consultation with the BMS Medical Monitor.
- Subjects who delay study treatment due to any Grade ≥ 3 amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis, and that is assessed by the investigator to be related to ipilimumab and not to nivolumab, may resume nivolumab when the amylase or lipase abnormality has resolved to Grade < 3. The 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 4.5.6.1.

4.5.5.2 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 4.5.6.2) should have treatment permanently discontinued.

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- 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.
- Dose delay of ipilimumab which results in no ipilimumab dosing for > 12 weeks requires ipilimumab discontinuation, with exceptions as noted in Section 4.5.6.2.
- Ipilimumab may not be resumed sooner than 6 weeks (+/- 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.

4.5.5.3 Criteria to Resume Treatment with Platinum Doublet Chemotherapy (Arms C, F and I)

- Subjects may resume treatment with platinum doublet chemotherapy when the ANC returns to ≥ 1500 µl, the platelet count returns to ≥ 100,000/mm^3, and all other drug-related toxicities have returned to baseline or Grade ≤ 1 (or Grade ≤ 2 for alopecia and fatigue).
- If a subject fails to meet criteria for 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 platinum doublet chemotherapy to baseline or Grade ≤ 1 (except Grade 2 alopecia and fatigue) within 6 weeks from the last dose given should discontinue the drug(s) that caused the delay.

When resuming platinum doublet chemotherapy treatment, please follow the dose reduction recommendations in Section 4.5.4.2.

4.5.5.4 Criteria to Resume Treatment with Nivolumab and Platinum Doublet Chemotherapy (Arms G and H)

- As noted in Section 4.5.3.4, dosing of all drugs in Arms G and H should be delayed if any criteria in sections 4.5.3.1 (Arm A, nivolumab monotherapy) or 4.5.3.3 or 4.5.3.4 (Arms

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C, F and I, platinum doublet chemotherapy) are met. That is, nivolumab should be delayed if criteria for delay of platinum doublet chemotherapy are met, and platinum doublet chemotherapy should be delayed if criteria for delay of nivolumab are met.

- Subjects in Arms G and H may resume dosing only when criteria for BOTH resumption of nivolumab (Section 4.5.5.1) AND platinum doublet chemotherapy (Section 4.5.5.3) are met. That is, nivolumab and platinum doublet chemotherapy must be administered together until treatment discontinuation criteria (Sections 4.5.6.1 and 4.5.6.3) or 4 cycles of platinum doublet chemotherapy have been completed, and maintenance therapy has been started.

4.5.6 Treatment Discontinuation Criteria

For all subjects in both parts 1 and 2, global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration' in the source data and in the case report form. Every effort should be made to document objective progression (i.e., radiographic confirmation) even after discontinuation of treatment.

4.5.6.1 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 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, hypersensitivity reaction, or infusion reaction **of any duration** requires discontinuation.
  Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation.
  Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
  Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation.
  Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation (also see Hepatic Adverse Event Management Algorithm):
  AST or ALT > 5-10x ULN for > 2 weeks
  AST or ALT > 10x ULN
  Total bilirubin > 5 x ULN

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Concurrent AST or ALT > 3 x ULN **and** total bilirubin > 2 x 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 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.
- 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.
- Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events 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 from the previous dose, the BMS medical monitor must be consulted.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.

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

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

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

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4.5.6.2 Ipilimumab Dose Discontinuation

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

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

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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. However, ipilimumab may not be continued as monotherapy as there is no evidence for its efficacy in this setting.

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

4.5.6.3 Platinum Doublet Chemotherapy Dose Discontinuation (Arms C, F, G, H and I)

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

- 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 cisplatin-related decrease in creatinine clearance to < 50 mL/min (using the Cockroft Gault formula) requires discontinuation of cisplatin.
- Any drug-related adverse event which recurs after two prior dose reductions for the same drug-related adverse event (as specified in Sections 4.5.4.3, 4.5.4.4, and 4.5.4.3) 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

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chemotherapy drugs being administered to any given subject for additional guidance on dose discontinuation.

- For subjects for whom it was indicated that maintenance pemetrexed therapy would be administered, 4 cycles of chemotherapy should be given prior to starting the maintenance treatment. However, subjects who experience grade 4 treatment-related hematologic toxicity, or grade 3 treatment-related non-hematologic toxicity, may start maintenance therapy after 3 cycles of chemotherapy. The nature and grade of the toxicity must be clearly noted, and the medical monitor must be notified.

Note that subjects receiving gemcitabine/cisplatin who discontinue cisplatin alone may, at the investigator's discretion, be switched to gemcitabine/carboplatin for the remainder of the platinum doublet cycles (up to 4 cycles in total). Subjects receiving pemetrexed/cisplatin who discontinue cisplatin alone may, at the investigator's discretion, be switched to pemetrexed/carboplatin for the remainder of the platinum doublet cycles (up to 4 cycles in total).

For subjects in Arms G and H, if the investigator is unable to determine whether an adverse event is due to nivolumab or to platinum doublet chemotherapy, then all drugs must be discontinued.

4.5.7 Treatment Beyond Disease Progression (Arms A, B, D, G and H)

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[23]

Subjects will be permitted to continue on nivolumab (Arms A, G and H) or nivolumab + ipilimumab (Arms B and D) for treatment beyond initial RECIST 1.1 defined PD as long as they meet the following criteria, for up to a 2 year total treatment duration:

- 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 (e.g., CNS metastases)
- **Subject provides written informed consent prior to receiving additional nivolumab and or ipilimumab treatment, using an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options**.

The decision to continue treatment beyond initial investigator-assessed progression 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 every twelve (12) weeks 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 to Table 5.1-4.

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For the subjects in Arms A, B, D, G, and H who continue study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden from time of initial PD. This includes an increase in the sum of diameters of all target lesions and/ or the diameters of new measurable lesions compared to the time of initial PD. Nivolumab and/or ipilimumab treatment should be discontinued permanently upon documentation of further progression.

New lesions are considered measureable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). Any new lesion considered non-measureable at the time of initial progression may become 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.

4.5.8 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

The above algorithms are found in both the nivolumab and ipilimumab Investigator Brochures, as well as in **Appendix 2**.

4.5.9 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:

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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 [e.g., 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 [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., 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.

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In case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., 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 (e.g., 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, i.e., 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.

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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.

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5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Assessments and Procedures (CA209227) - 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 during screening period and (re-enrollment, if applicable) prior to randomization
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). This is subject to medical monitor/MST Chair approval.

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Table 5.1-1: Screening Assessments and Procedures (CA209227) - 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, phosphorus, 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 randomization.
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 randomization. CT-chest, abdomen, pelvis & all known or suspected sites of disease should be assessed at baseline MRI of brain is preferred but CT scan is acceptable.
Biomarker Assessments		
Archived Tumor Tissue or Recent Tumor Biopsy	X	Section 5.6.1 and 3.3.1 Recent sample or archival, obtained within 6 months of 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 prior to randomization. An email communication will be sent to site for evaluable tumor tissue for PD-L1 expression status determination.
[redacted]		
EGFR Mutation ALK Translocation Status	X	Section 3.3.2 To be performed prior to randomization for all non-squamous subjects

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Table 5.1-1: Screening Assessments and Procedures (CA209227) - All Subjects

Procedure	Screening Visit	Notes
IVRS/Clinical Drug Supplies		
IVRS	X	Section 4.4 For subject number assignment at the time informed consent is obtained

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Table 5.1-2: On Study Assessments Treatment Phase-Arm A- Nivolumab Monotherapy (CA209227)[a]

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 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.
Review of Concomitant Medications	X	X			Section 3.4
Laboratory Tests	X	X (except TSH)		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, phosphorus, 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 regardless of dosing schedule.

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Table 5.1-2: On Study Assessments Treatment Phase-Arm A- Nivolumab Monotherapy (CA209227)[a]

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 purposes of this table, a cycle refers to the nivolumab every 2 weeks regimen.
Efficacy Assessments					
Radiographic Tumor Assessment (CT/MRI of chest, abdomen, pelvis)	**Section 4.5.7: For Treatment Beyond Progression** - 1st follow-up scan within six (6) weeks ± 5 days of original PD then subsequent scans every twelve (12) weeks until further progression. 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 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. NOTE: MRI of brain is preferred but CT scan is acceptable.				
[redacted]					
Pharmacokinetic (PK) and Immunogenicity Assessments					
PK Samples	Throughout the study				Section 5.5 & Table 5.5.1-1

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Table 5.1-2: On Study Assessments Treatment Phase-Arm A- Nivolumab Monotherapy (CA209227)[a]

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 purposes of this table, a cycle refers to the nivolumab every 2 weeks regimen.
Immunogenicity Samples	Throughout the study				Section 5.5 & Table 5.5.1-1
Patient Reported Outcomes Assessment (PRO)	X	X		X After 6 months	Section 5.7. For C1D1 - LCSS and EQ-5D assessments performed after randomization, PRIOR to first dose (day -3 to +1). For on-study visits: Assessments (LCSS and EQ-5D) will be performed PRIOR to treatment. Assessments will be performed at each cycle on Day 1 for the first 6 months on study, then every 6 weeks or every 3 cycles thereafter for the remainder of the **treatment period**
Health Resource Utilization		X			Except cycle 1. To include: concomitant medication collection Section 5.7.1
Clinical Drug Supplies					
IVRS Vial Assignment	X	X			Section 4.4. Within 1 business day prior to dosing
Nivolumab 240 mg q 2 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, for up to two years.

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Table 5.1-3: On Study Assessments Treatment Phase-Arms G - Nivolumab 360 mg + platinum-doublet chemotherapy q3w x 4 cycles combination (CA209227)[a]

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 + platinum-doublet chemotherapy every 3 weeks x4 cycles regimen and for the maintenance phase when it refers to nivolumab every 3 weeks.
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.
Review of Concomitant Medications	X	X			Section 3.4
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, phosphorus, glucose, amylase, lipase, TSH (with reflexive Free T4 and Free T3). Thyroid Function Testing to be evaluated every 6 weeks CBC required prior to gemcitabine dosing on Day 8 of each cycle. **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.

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Table 5.1-3: On Study Assessments Treatment Phase-Arms G - Nivolumab 360 mg + platinum-doublet chemotherapy q3w x 4 cycles combination (CA209227)[a]

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 + platinum-doublet chemotherapy every 3 weeks x4 cycles regimen and for the maintenance phase when it refers to nivolumab every 3 weeks.
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. **SUBSEQUENT** tumor assessments should occur every 6 weeks (± 7 days) up to first 12 months (week 48), then every 12 weeks until disease progression 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. NOTE: MRI of brain is preferred but CT Scan is acceptable.				
[redacted]					
Pharmacokinetic (PK) and Immunogenicity Assessments					
PK Samples	Throughout the study				Section 5.5 & Table 5.5.1-2
Immunogenicity Samples	Throughout the study				Section 5.5 & Table 5.5.1-2

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Table 5.1-3: On Study Assessments Treatment Phase-Arms G - Nivolumab 360 mg + platinum-doublet chemotherapy q3w x 4 cycles combination (CA209227)[a]

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 + platinum-doublet chemotherapy every 3 weeks x4 cycles regimen and for the maintenance phase when it refers to nivolumab every 3 weeks.
Patient Reported Outcomes Assessment (PRO)	X	X	X After 6 months		Section 5.7. For C1D1 - LCSS and EQ-5D assessments performed after randomization PRIOR to first dose (day -3 to +1). For on-study visits: Assessments (LCSS and EQ-5D) will be performed PRIOR treatment. Assessments will be performed at each cycle on Day 1 for the first 6 months on study, then every 6 weeks or every 2 cycles thereafter for the remainder of the **treatment period**
Health Resource Utilization		X			Except cycle 1. To include: concomitant medication collection. Section 5.7.1
Clinical Drug Supplies					
IVRS Vial Assignment	X	X			Section 4.4. Within 1 business day prior to dosing
Nivolumab 360 mg + platinum-doublet chemotherapy q 3w x4 cycles	X	X			Section 4.5 & Table 4.5-1
Maintenance Phase Dose Schedule					For the maintenance phase, subjects follow the same schedule of assessments as in the treatment phase.
Nivolumab 360 mg q 3 week [b]	X	X			Section 4.5 & Table 4.5-2.

[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)

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[b] continue until disease progression, discontinuation due to unacceptable toxicity, withdrawal of consent, or study closure, for up to two years.

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Table 5.1-4: On Study Assessments Treatment Phase-Arms B and D - Nivolumab 3 mg/kg q2 w + Ipilimumab 1mg/kg q6 w combination (CA209227)[a]

Procedure	Cycle 1 Day 1	Each Subsequent Cycle Day1 (± 3 Days)	Every 2 Cycles Day 1 (± 3 Days)	Every 3 Cycles Day 1 (± 5 Days)	Notes For the purposes of this table, a cycle refers to nivolumab every 2 weeks.
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.
Review of Concomitant Medications	X	X			Section 3.4
Laboratory Tests	X	X (except TSH)		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, phosphorus, 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 regardless of dosing schedule

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Table 5.1-4: On Study Assessments Treatment Phase-Arms B and D - Nivolumab 3 mg/kg q2 w + Ipilimumab 1mg/kg q6 w combination (CA209227)[a]

Procedure	Cycle 1 Day 1	Each Subsequent Cycle Day1 (± 3 Days)	Every 2 Cycles Day 1 (± 3 Days)	Every 3 Cycles Day 1 (± 5 Days)	Notes For the purposes of this table, a cycle refers to nivolumab every 2 weeks.
Efficacy Assessments					
Radiographic Tumor Assessment (CT/MRI of chest, abdomen, pelvis)	Section 4.5.7: **For Treatment Beyond Progression** - 1st follow-up scan within six (6) weeks ± 5 days of original PD then subsequent scans every twelve (12) weeks until further progression. 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 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. NOTE: MRI of brain is preferred but CT scan is acceptable.				
[redacted]					
Pharmacokinetic (PK) and Immunogenicity Assessments					
PK Samples	Throughout the study				Section 5.5 & Table 5.5.1-3

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Table 5.1-4: On Study Assessments Treatment Phase-Arms B and D - Nivolumab 3 mg/kg q2 w + Ipilimumab 1mg/kg q6 w combination (CA209227)[a]

Procedure	Cycle 1 Day 1	Each Subsequent Cycle Day1 (± 3 Days)	Every 2 Cycles Day 1 (± 3 Days)	Every 3 Cycles Day 1 (± 5 Days)	Notes For the purposes of this table, a cycle refers to nivolumab every 2 weeks.
Immunogenicity Samples	Throughout the study				Section 5.5 & Table 5.5.1-3
Patient Reported Outcomes Assessment (PRO)	X	X		X After 6 months	Section 5.7. For C1D1 - LCSS and EQ-5D assessments performed after randomization PRIOR to first dose (day -3 to +1). For on-study visits: Assessments (LCSS and EQ-5D) will be performed PRIOR to treatment. Assessments will be performed at each cycle on Day 1 for the first 6 months on study, then every 6 weeks or every 3 cycles thereafter for the remainder of the **treatment period**
Health Resource Utilization		X			Except cycle 1. To include: concomitant medication collection Section 5.7.1
Clinical Drug Supplies					
IVRS Vial Assignment	X	X			Section 4.4 Within 1 business day prior to dosing
Nivolumab 3 mg/kg q 2 weeks + Ipilimumab 1 mg/kg q 6 weeks[b]	X	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, for up to two years.

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Table 5.1-5: On Study Assessments Treatment Phase-Arms C and F - Platinum-doublet chemotherapy (CA209227)[a]

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 purposes of this table, a cycle refers to the platinum doublet chemotherapy every 3 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 Monitoring for adverse events related to chemotherapy drugs in Arm C and F subjects should follow recommendations specified in the local labels. SAEs should be approved in Trial Access Online (TAO) within 5 days from entry.
Review of Concomitant Medications	X	X			Section 3.4
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, phosphorus, glucose, amylase, lipase, TSH (with reflexive Free T4 and Free T3). Thyroid Function Testing to be evaluated every 6 weeks. CBC required prior to gemcitabine dosing on Day 8 of each cycle. **Note:** C1D1 labs do not need to be repeated if they were performed within 14 days of dosing.

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Table 5.1-5: On Study Assessments Treatment Phase-Arms C and F - Platinum-doublet chemotherapy (CA209227)[a]

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 purposes of this table, a cycle refers to the platinum doublet chemotherapy every 3 weeks regimen.
Pregnancy Test (WOCBP only)	X	X			Section 5.3.2 To be evaluated at least every 3 weeks regardless of dosing schedule
Efficacy Assessments					
Radiographic Tumor Assessment (CT/MRI of chest, abdomen, 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 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. NOTE: MRI of brain is preferred but CT Scan is acceptable.				

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Table 5.1-5: On Study Assessments Treatment Phase-Arms C and F - Platinum-doublet chemotherapy (CA209227)[a]

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 purposes of this table, a cycle refers to the platinum doublet chemotherapy every 3 weeks regimen.
Patient Reported Outcomes Assessment (PRO)	X	X	X After 6 months		Section 5.7. For C1D1 - LCSS and EQ-5D assessments performed after randomization PRIOR to first dose (day -3 to +1). For on-study visits: Assessments (LCSS and EQ-5D) will be performed PRIOR to treatment. Assessments will be performed at each cycle on Day 1 for the first 6 months on study, then every 6 weeks or every 2 cycles thereafter for the remainder of the **treatment period**
Health Resource Utilization		X			Except cycle 1. To include: concomitant medication collection Section 5.7.1
Clinical Drug Supplies					
IVRS Vial Assignment	X	X			Section 4.4. Within 1 business day prior to dosing
Platinum doublet Chemotherapy	X	X			See section 4.5. For Platinum doublet chemotherapy options & dose levels, refer to Table 4.5-1 and Table 4.5-2. Gemcitabine will be provided on day 1 and day 8 of each dosing cycle.

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Table 5.1-5: On Study Assessments Treatment Phase-Arms C and F - Platinum-doublet chemotherapy (CA209227)[a]

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 purposes of this table, a cycle refers to the platinum doublet chemotherapy every 3 weeks regimen.
Maintenance Phase Dose Schedule: Optional maintenance Pemetrexed for nonsquamous histology subjects only					For the maintenance phase, subjects follow the same schedule of assessments as in the treatment phase.
Pemetrexed 500 mg/m^2	Week 1 Day 1 and Week 4 Day 1				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)

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Table 5.1-6: Follow-up and Survival Procedures (CA209227) - 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.
Review of Concomitant Medications	X		Section 3.4.
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/MRI of chest, abdomen, 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. *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. NOTE: MRI of brain is preferred but CT scan is acceptable.
Patient Reported Outcomes Assessment (PRO)	X	EQ-5D only	Both the LCSS and EQ-5D will be given in FU Visits 1 & 2. In Survival Visits, EQ-5D is collected every 3 months for the first year of the Follow-Up Phase, then every 6 months thereafter.

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Table 5.1-6: Follow-up and Survival Procedures (CA209227) - All subjects

Procedure	Follow-Up Visits 1 & 2[a]	Survival Follow-up Visits[b]	Notes
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. Additional subsequent cancer therapy details such as regimen, setting of the regimen, line of therapy, start date and end date of each regimen, best response to the regimen and date of progression after second line therapy will be collected.

[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 80 days from Follow-Up Visit 1 (± 7 days).

[b] Survival Follow-Up Visits to occur approximately every 3 months (± 7 days) from Follow-Up Visit 2.

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Table 5.1-7: On Study Assessments Treatment Phase-Arms H - Nivolumab 360 mg + platinum-doublet chemotherapy q3w x 4 cycles combination (CA209227) [a]

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 + platinum-doublet chemotherapy every 3 weeks x4 cycles regimen and for the maintenance phase when it refers to nivolumab every 3 weeks.
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.
Review of Concomitant Medications	X	X			Section 3.4
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, phosphorus, 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.

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Table 5.1-7: On Study Assessments Treatment Phase-Arms H - Nivolumab 360 mg + platinum-doublet chemotherapy q3w x 4 cycles combination (CA209227) [a]

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 + platinum-doublet chemotherapy every 3 weeks x4 cycles regimen and for the maintenance phase when it refers to nivolumab every 3 weeks.
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. **SUBSEQUENT** tumor assessments should occur every 6 weeks (± 7 days) up to first 12 months (week 48), then every 12 weeks until disease progression 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. NOTE: MRI of brain is preferred but CT scan is acceptable.				

[redacted]

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Table 5.1-7: On Study Assessments Treatment Phase-Arms H - Nivolumab 360 mg + platinum-doublet chemotherapy q3w x 4 cycles combination (CA209227) [a]

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 + platinum-doublet chemotherapy every 3 weeks x4 cycles regimen and for the maintenance phase when it refers to nivolumab every 3 weeks.
[redacted]					
Pharmacokinetic (PK) and Immunogenicity Assessments					
PK Samples	Throughout the study				Section 5.5 & Table 5.5.1-1
Immunogenicity Samples	Throughout the study				Section 5.5 & Table 5.5.1-1
Patient Reported Outcomes Assessment (PRO)	X	X	X After 6 months		Section 5.7. For C1D1 - LCSS and EQ-5D assessments performed after randomization PRIOR to first dose (day -3 to +1). For on-study visits: Assessments (LCSS and EQ-5D) will be performed PRIOR treatment. Assessments will be performed at each cycle on Day 1 for the first 6 months on study, then every 6 weeks or every 2 cycles thereafter for the remainder of the **treatment period**
Health Resource Utilization		X			Except cycle 1. To include: concomitant medication collection. Section 5.7.1
Clinical Drug Supplies					
IVRS Vial Assignment	X	X			Section 4.4. Within 1 business day prior to dosing
Nivolumab 360 mg + platinum-doublet chemotherapy q 3w x4 cycles	X	X			Section 4.5 & Table 4.5-1

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Table 5.1-7: On Study Assessments Treatment Phase-Arms H - Nivolumab 360 mg + platinum-doublet chemotherapy q3w x 4 cycles combination (CA209227) [a]

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 + platinum-doublet chemotherapy every 3 weeks x4 cycles regimen and for the maintenance phase when it refers to nivolumab every 3 weeks.
Maintenance Phase Dose Schedule					For the maintenance phase, subjects follow the same schedule of assessments as in the treatment phase.
Nivolumab 360 mg q 3 week [b]	X	X			Section 4.5 & Table 4.5-2.

[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] continue until disease progression, discontinuation due to unacceptable toxicity, withdrawal of consent, or study closure, for up to two years

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Table 5.1-8: On Study Assessments Treatment Phase-Arm I- Platinum-doublet chemotherapy (CA209227)[a]

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 purposes of this table, a cycle refers to the platinum doublet chemotherapy every 3 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 Monitoring for adverse events related to chemotherapy drugs in Arm I subjects should follow recommendations specified in the local labels. SAEs should be approved in Trial Access Online (TAO) within 5 days from entry.
Review of Concomitant Medications	X	X			Section 3.4
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, phosphorus, 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			Section 5.3.2 To be evaluated at least every 3 weeks regardless of dosing schedule

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Table 5.1-8: On Study Assessments Treatment Phase-Arm I- Platinum-doublet chemotherapy (CA209227)[a]

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 purposes of this table, a cycle refers to the platinum doublet chemotherapy every 3 weeks regimen.
Efficacy Assessments					
Radiographic Tumor Assessment (CT/MRI of chest, abdomen, 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 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. NOTE: MRI of brain is preferred but CT scan is acceptable.				

[redacted]

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Table 5.1-8: On Study Assessments Treatment Phase-Arm I- Platinum-doublet chemotherapy (CA209227)[a]

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 purposes of this table, a cycle refers to the platinum doublet chemotherapy every 3 weeks regimen.
Patient Reported Outcomes Assessment (PRO)	X	X	X After 6 months		Section 5.7. For C1D1 - LCSS and EQ-5D assessments performed after randomization PRIOR to first dose (day -3 to +1). For on-study visits: Assessments (LCSS and EQ-5D) will be performed PRIOR to treatment. Assessments will be performed at each cycle on Day 1 for the first 6 months on study, then every 6 weeks or every 2 cycles thereafter for the remainder of the **treatment period**
Health Resource Utilization		X			Except cycle 1. To include: concomitant medication collection Section 5.7.1
Clinical Drug Supplies					
IVRS Vial Assignment	X	X			Section 4.4. Within 1 business day prior to dosing
Platinum doublet Chemotherapy	X	X			See section 4.5. For Platinum doublet chemotherapy options & dose levels, refer to Table 4.5-1 and Table 4.5-2.

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Table 5.1-8: On Study Assessments Treatment Phase-Arm I- Platinum-doublet chemotherapy (CA209227)[a]

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 purposes of this table, a cycle refers to the platinum doublet chemotherapy every 3 weeks regimen.
Maintenance Phase Dose Schedule: Optional maintenance Pemetrexed for nonsquamous histology subjects only					For the maintenance phase, subjects follow the same schedule of assessments as in the treatment phase.
Pemetrexed 500 mg/m^2	Week 1 Day 1 and Week 4 Day 1				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)

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5.1.1 Retesting During Screening

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

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

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, [redacted] and immunogenicity) and tissue specimens
- Site manual for operation of interactive voice response system, including enrollment/randomization worksheets
- Manual for entry of local laboratory data
- Pregnancy Surveillance Forms
- RECIST 1.1 pocket guide
- CA209227 study Imaging Manual
- Lung Cancer Symptom Scale and EuroQol Group's EQ-5D questionnaires

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), temperature, and oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable) should be performed within 28 days prior to first dose. Baseline signs and symptoms are those that are assessed within 14 days prior to first dose. Concomitant medications will be collected from 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, phosphorous, 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 randomization: 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 for subjects assigned to arms A, B, D and **every 3 weeks (each cycle)** ± 3 days for subjects (for subjects assigned to arms C, F, G, H and I). Pregnancy testing must be within 24 hours prior to Day 1 of each treatment cycle (prior to dosing).

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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, phosphorous, LDH, glucose, amylase, and lipase. Thyroid function (TSH only) 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 5.1-6) 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. Oxygen saturation by pulse oximetry at rest and on exertion (also monitor amount of supplemental oxygen if applicable) should be assessed at each on-study visit prior to dosing. 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 (e.g., suspected drug induced liver enzyme evaluations) will be monitored during the follow-up phase via on site/local labs until all study drug related toxicities resolve, return to baseline, or are deemed irreversible.

Oxygen saturation by pulse oximetry should be obtained prior to each dosing and at any time a subject has any new or worsening respiratory symptoms. A reading at rest and on exertion should be obtained at each time point. The extent of the exertion should be based on the judgment of the investigator, but should remain consistent for each individual subject throughout the study. If the patient's subject's status changes, the investigator can alter the extent of exertion based on their medical judgment. If a subject shows changes on pulse oximetry or other pulmonary related signs (hypoxia, fever) or symptoms (e.g., dyspnea, cough, and fever) consistent with possible pulmonary adverse events, the patient subject should be immediately evaluated to rule out pulmonary toxicity. An algorithm for the management of suspected pulmonary toxicity can be found in the nivolumab Investigator's Brochure and in the protocol appendix (appendix 2).

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

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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

Study evaluations (tumor assessments) will take place in accordance with the tables in Section 5.1. Images will be submitted to an imaging corelab for central review. Sites will be trained prior to scanning the first study subject. Image acquisition guidelines and submission process will be outlined in the CA209227 study Imaging Manual to be provided by the corelab. Contrast enhanced CT with PO/IV contrast or contrast enhanced MRI are the preferred imaging modalities for assessing radiographic tumor response. NOTE: A Brain MRI is preferred but CT scan is acceptable. If a subject has a known allergy to contrast material, please use local prophylaxis standards to obtain the assessment with contrast if at all possible, or use the alternate modality. In cases where contrast is strictly contraindicated, a non-contrast scan will suffice. Should a subject have a contraindication for CT IV contrast, a non-contrast CT of the chest and a contrast enhanced MRI of the abdomen and pelvis may be obtained. Every attempt should be made to image each subject using an identical acquisition protocol on the same scanner for all imaging time points.

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

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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 preferred but CT scan is acceptable 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.

Baseline tumor assessments must be performed within 28 days prior to randomization. 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. NOTE: A Brain MRI is preferred but CT scan is acceptable.

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. At the time of investigator-assessed disease progression, the site must request an Independent Review of Progression from the third-party radiology vendor, as specified in Section 7.2.

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.

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

If clinically acceptable, subsequent therapy should begin only after RECIST 1.1 progression has been assessed by central review upon Independent Review of Progression. Subjects who start palliative local therapy or subsequent therapy without prior assessment of RECIST 1.1 progression by central review, the Independent Review of Progression must continue tumor assessments (if clinically feasible) according to the protocol-specified schedule and submit them to the third-party radiology vendor. When RECIST 1.1 progression is assessed by the investigator (whether assessed before or after the start of palliative local therapy or subsequent therapy), the central Independent Review of Progression must be requested. Tumor assessments may be discontinued when the independent radiologist assesses the subject to have met RECIST 1.1 criteria for progression.

5.4.1 Primary Efficacy Assessment

Overall survival and PFS assessed by BICR are the primary endpoints for Part 1 and OS is the primary endpoint for Part 2 of the study. See Section 8.3.1 for the definitions of OS and PFS. Every effort will be made to collect survival data on all subjects including subjects withdrawn from treatment for any reason, who are eligible to participate in the study and who have not withdrawn consent for survival data collection. If the death of a subject is not reported, all dates in this study representing a date of subject contact will be used in determination of the subject's last known date alive.

5.4.2 Secondary Efficacy Assessment

Overall response rate, based on BICR assessment, is a secondary efficacy endpoint for Part 2 and exploratory endpoint for Part 1. See Section 8.3.2 for the definition of ORR. All randomized subjects will be monitored by radiographic assessment on an every-6-week schedule every 6 weeks (± 7 days) for the first 12 months (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.

For details regarding response criteria using RECIST 1.1 refer to **Appendix 3.**

5.5 Pharmacokinetic and Immunogenicity Assessments

Samples for PK and immunogenicity assessments will be collected for all subjects receiving nivolumab and ipilimumab as described in Table 5.5.1-1 to Table 5.5.1-3. All time points are relative to the start of study drug administration. All on-treatment time points are intended to align with days on which study drug is administered, if dosing occurs on a different day, the PK and immunogenicity sampling should be adjusted accordingly. Further details of sample collection, processing, and shipment will be provided in the laboratory procedures manual.

5.5.1 Pharmacokinetic and Immunogenicity Collection and Processing

A detailed schedule of PK and immunogenicity evaluations is provided in Table 5.5.1-1 to Table 5.5.1-3. PK samples will be analyzed for nivolumab/ipilimumab by a validated ligand binding assay. Immunogenicity samples will be analyzed for anti-nivolumab antibodies / anti-ipilimumab antibodies by a validated immunogenicity assay; samples may also be analyzed for neutralizing

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antibodies by a validated method. Serum samples may be analyzed by an exploratory method that measures anti-drug antibodies for technology exploration purposes; exploratory results will not be reported. Serum samples designated for PK or [redacted] assessments may also be used for immunogenicity analysis if required (e.g., insufficient volume for complete immunogenicity assessment or to follow up on suspected immunogenicity related AE).

Table 5.5.1-1: Pharmacokinetic (PK) and Immunogenicity Sample Collections - Nivolumab Arm A

Study Day (1 Cycle = 2 Weeks)	Event (Relative To Dosing) Hour	Time (Relative To Dosing) Hour: Min	Pharmacokinetic Blood Sample for Nivolumab	Immunogenicity Blood Sample for Nivolumab
C1D1	Predose[a]	00:00	X	X
C2D1	Predose[a]	00:00	X	X
C4D1	Predose[a]	00:00	X	X
C10D1	Predose[a]	00:00	X	X
D1 of every 9th cycle after C10 D1 until discontinuation of study treatment or maximum up to 2 years of treatment	Predose[a]	00:00	X	X

[a] Predose samples for nivolumab should be taken prior to the start of nivolumab infusion (preferably within 30 minutes). If it is known that a dose is going to be delayed, then predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected, but the dose is subsequently delayed, an additional predose sample should not be collected.

Table 5.5.1-2: Pharmacokinetic (PK) and Immunogenicity Sample Collections - Nivolumab + platinum doublet chemotherapy Arm G and H

Part[a]	Study Day 1 Cycle = 3 Weeks	Event (Relative To Dosing) Hour	Time (Relative To Dosing) Hour: Min	Pharmacokinetic Blood Sample for Nivolumab	Immunogenicity Blood Sample for Nivolumab
A	C1D1	Predose[b]	00:00	X	X
A	C2D1	Predose[b]	00:00	X	X
B	C5D1	Predose[b]	00:00	X	X
B	C10D1	Predose[b]	00:00	X	X

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Table 5.5.1-2: Pharmacokinetic (PK) and Immunogenicity Sample Collections - Nivolumab + platinum doublet chemotherapy Arm G and H

Part[a]	Study Day 1 Cycle = 3 Weeks	Event (Relative To Dosing) Hour	Time (Relative To Dosing) Hour: Min	Pharmacokinetic Blood Sample for Nivolumab	Immunogenicity Blood Sample for Nivolumab
B	D1 of every 9th Cycle after C10D1 until discontinuation of study treatment or maximum up to 2 years of treatment	Predose[b]	00:00	X	X

[a] Part A indicates first 12 weeks of treatment (nivolumab + platinum doublet chemotherapy dosing). Part B indicates nivolumab monotherapy period starting from Week 13

[b] Predose samples should be collected just before the administration of the first drug (preferably within 30 minutes). If it is known that a dose is going to be delayed, then predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected, but the dose is subsequently delayed, an additional predose sample should not be collected.

Table 5.5.1-3: Pharmacokinetic (PK) and Immunogenicity Sample Collections - Nivolumab + Ipilimumab Arms B and D

Study Day[a] (1 Cycle = 2 weeks)	Event (Relative To Dosing) Hour	Time (Relative To Dosing) Hour: Min	Pharmacokinetic Blood Sample for Nivolumab	Immunogenicity Blood Sample for Nivolumab	Pharmacokinetic Blood Sample for Ipilimumab	Immunogenicity Blood Sample for Ipilimumab
C1D1 (Ipilimumab dose 1)	Predose[b]	00:00	X	X	X	X
C2D1 (Nivolumab dose 2)	Predose[b]	00:00	X	X	X	X
C4D1 (Ipilimumab dose 2)	Predose[b]	00:00	X	X	X	X
C10D1 (Ipilimumab dose 4)	Predose[b]	00:00	X	X	X	X

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Table 5.5.1-3: Pharmacokinetic (PK) and Immunogenicity Sample Collections - Nivolumab + Ipilimumab Arms B and D

Study Day[a] (1 Cycle = 2 weeks)	Event (Relative To Dosing) Hour	Time (Relative To Dosing) Hour: Min	Pharmacokinetic Blood Sample for Nivolumab	Immunogenicity Blood Sample for Nivolumab	Pharmacokinetic Blood Sample for Ipilimumab	Immunogenicity Blood Sample for Ipilimumab
D1 of every 9th cycle after C10D1 until discontinuation of study treatment (or Ipilimumab Dose 7, 10, 13...etc.) or maximum up to 2 years of treatment	Predose[b]	00:00	X	X	X	X

[a] If ipilimumab is discontinued and nivolumab continues, ipilimumab PK and ADA should be collected only for the next 2 time points (corresponding to nivolumab sample collection) according to the PK table.

[b] Predose samples should be collected just before the administration of the nivolumab (preferably within 30 minutes). If it is known that a dose is going to be delayed, then predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected, but the dose is subsequently delayed, an additional predose sample should not be collected.

5.6 Biomarker Assessments

5.6.1 Tumor Tissue Specimens

Archival (or fresh) FFPE tumor tissue collected within 6 months prior to enrollment must be sent to a third party laboratory for determination of PD-L1 status using the analytically validated IHC assay. PD-L1 stained tissue samples will be assessed by a pathologist at a central lab identified by the Sponsor and scored as PD-L1 expressing if membrane staining is observed in ≥ 1% tumor cells among a minimum of 100 evaluable tumor cells. An email communication will be sent to site for evaluable tumor tissue for PD-L1 expression status determination. [redacted]

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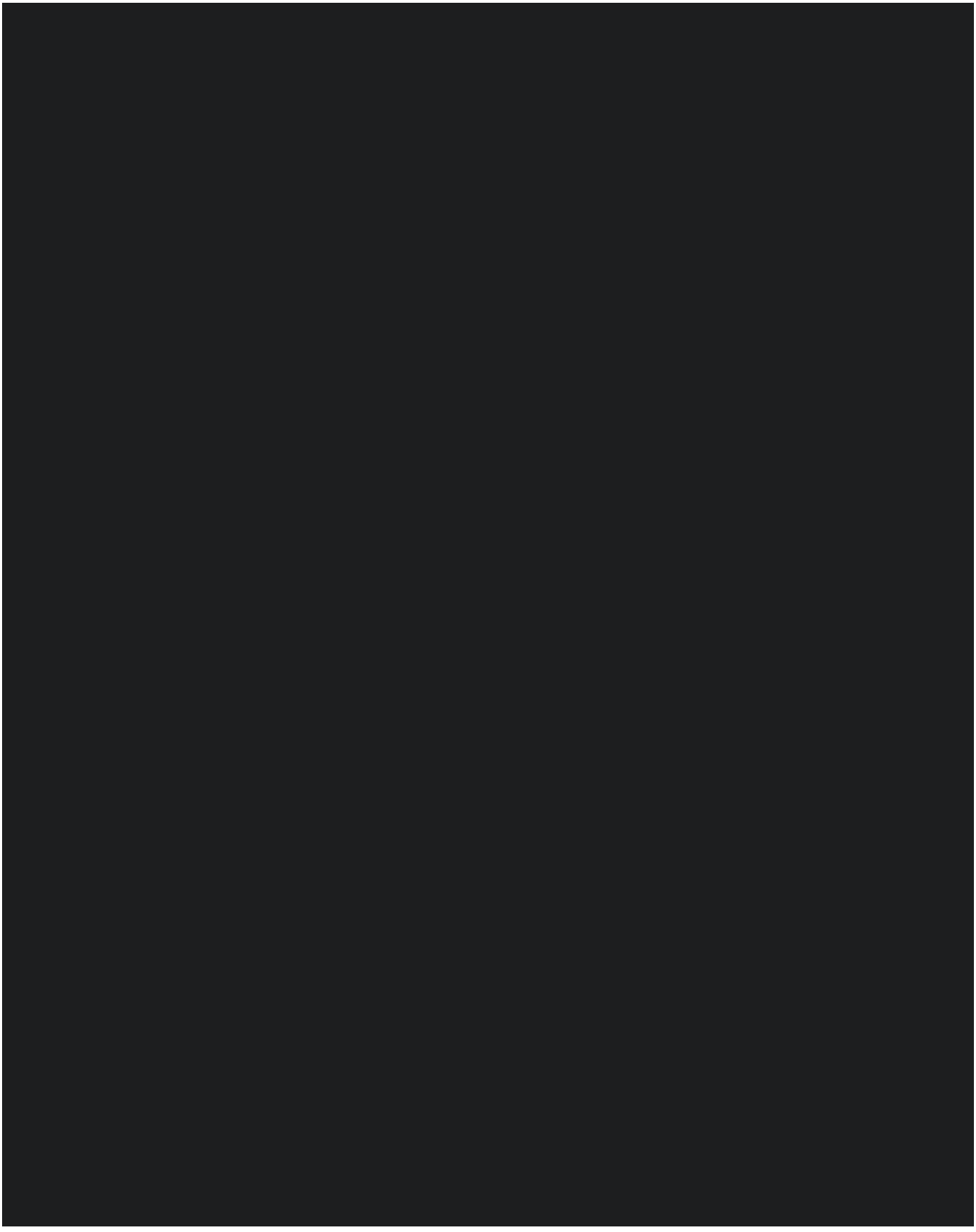

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5.7 Outcomes Research Assessments

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

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

General health status will be measured using the EQ-5D. The EQ-5D is a standardized instrument for use as a measure of self-reported health status. The EQ-5D comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety) and a visual analog rating scale (VAS). The utility data generated from the EQ-5D is recommended for and commonly used in cost effectiveness analysis.

5.7.1 Healthcare Resource Utilization

Healthcare resource utilization data (e.g., hospitalizations, non-protocol specified medical visits, etc.) will be collected for all randomized subjects. Specifically, healthcare resource utilization is evaluated based on the number of medical care encounters such as hospital admissions and their duration, outpatient visits, diagnostic tests and procedures, concomitant medications and reasons for the encounters.

Resource utilization questions will be asked during the study and at the two follow up visits as outlined in Table 5.1-2, Table 5.1-3, Table 5.1-4, Table 5.1-5, and Table 5.1-6.

5.8 Other Assessments

5.8.1 Immunogenicity Assessments

Blood samples for immunogenicity analyses of nivolumab and ipilimumab will be collected according to the schedule given in Table 5.5.1-1 to Table 5.5.1-3. Samples collected from subjects in each treatment arm will be evaluated for development of Anti-Drug Antibody (ADA) for nivolumab/ipilimumab by validated immunoassays. Samples may also be analyzed for neutralizing ADA response to nivolumab/ipilimumab.

5.9 Results of Central Assessments

Site will be informed of quality issues or needs for repeat scanning via queries from the core lab. Results of Central Imaging analysis will not be returned to the site.

5.10 Subjects who are Randomized but Never Treated

Every effort should be made to avoid randomizing subjects who will not be treated. All randomized subjects will be evaluated for efficacy analysis. However, for those subjects who are randomized but never treated, a minimal amount of data must be collected: all baseline data, AEs/SAEs, off-treatment reason and subject status. Efficacy assessments, including OS and tumor assessments until progression by BICR, should be collected.

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

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does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.

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

Related: There is a reasonable causal relationship between study drug administration and the AE.

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

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

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

6.1 Serious Adverse Events

A 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 [e.g., 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 (e.g., 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).

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Any component of a study endpoint that is considered related to study therapy (e.g., 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 (e.g., 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 (e.g., 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 the last dose of study drug**.** Subjects, who are randomized and never treated with study drug, must have SAEs collected for 30 days from the date of randomization. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy).

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

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

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

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours of awareness of 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

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forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

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

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

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

All SAEs should be followed to resolution or stabilization.

6.2 Nonserious Adverse Event Collection and Reporting

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

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

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

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.

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 (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE

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- 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 (e.g., 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 (e.g., dose tapering if necessary for subject safety).

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

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., 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 SAEs (see Section 6.1.1 for reporting details).

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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 occurring within 100 days of the last dose, regardless of causality, with no clear alternate etiology based on investigator assessment, with data collected on a new CRF page
- Events treated with immune-modulating medication. (Note: adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis are considered IMAEs regardless of immune-modulating medication use, since endocrine events are often managed without immune-modulating medication)

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

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

7.1 Data Monitoring Committee

A Data Monitoring Committee (DMC) will be utilized to provide general oversight and safety considerations for this study, CA209227. The DMC will provide advice to the Sponsor regarding actions the committee deems necessary for the continuing protection of subjects enrolled in this study. The DMC will be charged with assessing such actions in light of an acceptable risk/benefit profile for nivolumab. The DMC will act in an advisory capacity to BMS and will monitor subject safety data for the study.

The DMC will be advisory to the clinical study leadership team. The clinical study leadership will have responsibility for overall conduct of the study including managing the communication of study data. The group will be responsible for promptly reviewing the DMC recommendations, for providing guidance regarding the continuation or termination of the study, and for determining whether amendments to the protocol or changes to the study conduct are required.

The data monitoring committee will conduct a safety assessment after the first 20 patients in arms B and D have been treated and followed for 2 cycles.

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

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

At the time of investigator-assessed initial radiographic progression per RECIST 1.1 in any given subject, the site must request the blinded Independent Review of Progression from the third party radiology vendor. The investigator should not wait for the assessment of the Independent Review of Progression to make a treatment decision. Treatment decisions should only be based on Investigator assessment.

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

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

In Part 1 of the study, the overall enrolled population meeting the inclusion/exclusion criteria is categorized into PD-L1 expression level defined parts: PD-L1 expressing as Part 1A and PD-L1 non-expressing (<1%) as Part 1B. Subjects categorized within these pre-defined groups are then stratified by their histology status and randomized to the respective treatment arms in 1:1:1 ratio. The alpha (type-1 error) for assessing the co-primary and salient secondary objectives within Part 1 is set at two sided 0.05 level.

In Part 2 of the study, subjects meeting the inclusion/exclusion criteria regardless of PD-L1 expression level are randomized after the conclusion of enrollment and randomization of Part 1. Subjects are stratified by histology status, PD-L1 expression level and gender and randomized to the respective treatment arms in 1:1 ratio. The sample size is prospectively specified and the alpha for assessing the primary and secondary efficacy objectives in Part 2 is set at a two sided 0.05 level independently from Part 1.

A total of 1740 subjects are planned to be randomized into Part 1A and Part 1B of this study, with approximately 1200 PD-L1 expressing subjects randomized at 1:1:1 ratio into the respective treatment arms (Arms A, B, and C) and approximately 540 PD-L1 non-expressing subjects randomized into the respective treatment arms (Arms D, F, and G). Assuming a 35% screening failure rate, it is estimated that approximately 2677-subjects will be enrolled in order to have 1740 subjects randomized.

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A total of approximately 750 subjects are planned to be randomized into Part 2 of this study at 1:1 ratio to treatment arms (Arms H and I). Assuming a 35% screening failure rate, it is estimated that approximately 1153 subjects will be enrolled in order to have approximately 750 subjects randomized.

8.1.1 Sample size justification in Part 1A of the Study

8.1.1.1 Sample size justification to support co-primary objective of OS comparison of Arm B vs. Arm C in Part 1A

The sample size of Part 1A is calculated to compare OS between nivolumab in combination with ipilimumab (Arm B) and platinum doublet chemotherapy (Arm C) under a two-side 0.025 type I error with 90% power consideration for subjects with PD-L1 expressing (PD-L1 ≥1%). The number of events was estimated assuming an exponential distribution for OS in each arm.

Approximately 1200 subjects will be randomized to the 3 treatment groups (Arms A, B and C) in a 1:1:1 ratio. Approximately 553 events (i.e., deaths), observed among approximately 800 subjects between Arm B and C provides 90% power to detect a hazard ratio (HR) of 0.74 with a type I error of 0.025 (two-sided). The HR of 0.74 corresponds to a 35% increase in the median OS, assuming a median OS of 13.8 months for platinum doublet chemotherapy (arm C) and 18.6 months for nivolumab in combination with ipilimumab (Arm B) respectively. One interim OS analyses is planned at 70% of total events (i.e., 387 events) observed at final analysis The stopping boundaries at the interim and final analyses will be based on the actual number of OS events at the time of the analysis using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. If the interim analysis is performed exactly at 387 events, the nominal significance level for OS superiority will be 0.006. The nominal significance level for the final look of OS after 553 events would then be 0.023.

Assuming a piecewise accrual rate (number of randomized subjects per month: 1 for the first four months, 27 for the next 3 months and followed by 120 subsequently) for PD-L1 expressing subjects, it will approximately take 40 months (18 months for accrual and 22 months for follow-up) from the randomization of the first subject to observe the required number of events among subjects randomized to Arm B and C for final OS analysis. The number of events needed for the analyses will be monitored by the un-blinded independent statistician supporting the DMC.

Table 8.1.1.1-1 summarizes the key parameters of the sample size justification in Part 1A of the study.

Table 8.1.1.1-1: Summary of Sample Size Parameters and Schedule of Analyses in Part 1A of the Study

Primary Endpoint	**OS**
Primary analysis population	PD-L1 expressing ≥ 1% in Arm B and Arm C
Power (interim analysis / final analysis)	90% (58%/32%)
Alpha	0.025

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Table 8.1.1.1-1: Summary of Sample Size Parameters and Schedule of Analyses in Part 1A of the Study

Primary Endpoint	OS
Hypothesized Median OS (months): Chemotherapy(Arm C) vs. nivolumab + ipilimumab (Arm B)	13.8 vs. 18.6
Hypothesized Hazard ratio	0.74
Accrual Duration (months)	18
Timing of OS final analysis(from randomization of first subject (months)	40
Sample size (Arm B and Arm C)	800
Expected number of events for	
OS interim analysis (70% events)	387
OS final analysis	553

8.1.1.2 Sample size justification to support co-primary objective of PFS comparison of nivolumab + ipilimumab vs. chemotherapy in subjects with baseline high TMB regardless of PD-L1 expression

Approximately 221 PFS events observed among the high TMB subjects provides 80% power to detect a hazard ratio of 0.66 (nivolumab + ipilimumab vs. chemotherapy) with a two-sided type 1 error of 0.025. The HR of 0.66 corresponds to a 52% increase in the median PFS, assuming a median of 6 months for platinum doublet chemotherapy and 9.1 months for nivolumab in combination of ipilimumab. A HR of 0.66 is targeted based on observations from Checkmate 026, as well as based on what would be considered a clinically meaningful improvement in a biomarker-selected population. No formal interim analysis of PFS is planned. To achieve 221 PFS events, a sample size of at least 265 subjects will be required.

Assuming a piecewise accrual rate with a18-month accrual period, it will take approximately 25 months from the randomization of the first subject to observed the required number of events for PFS analysis. The number of events needed for the analyses will be monitored by the un-blinded independent statistician supporting the DMC.

Table 8.1.1.2-1 summarizes the key parameters of the sample size justification in the part 1 of the study.

Table 8.1.1.2-1: Sample Size Justification in Part 1 of the Study

Primary Endpoint	PFS
Primary analysis Comparison population	Subjects with TMB high nivolumab+ipilimumab (Pooled Arm B and Arm D) and chemotherapy (pooled Arm C and Arm F)
Power	80%

Table 8.1.1.2-1: Sample Size Justification in Part 1 of the Study

Primary Endpoint	**PFS**
Alpha	0.025
Hypothesized Median PFS of chemotherapy (pooled Arm C and Arm F) vs. nivolumab+ipilimumab (pooled Arm B and Arm D)	6 vs. 9.1
Hypothesized Hazard ratio	0.66
Accrual Duration (months)	18
Timing of final analysis (FA) from randomization of first subject (months)	25
Estimated sample size	At least 265
Expected number of events for final analysis	221

8.1.2 Sample size justification for part 2 of the study

The sample size of part 2 of the study accounts for

- primary objective comparison of OS between: nivolumab in combination with chemotherapy (Arm H) and platinum doublet chemotherapy (Arm I) among subjects with non-squamous histology at randomization as stratified
- key secondary objective comparison of OS between: nivolumab in combination with chemotherapy (Arm H) and platinum doublet chemotherapy (Arm I),among all randomized subjects

Approximately 750 subjects will be randomized to the 2 treatment groups in a 1:1 ratio, stratified by the PD-L1 expression level (< 1% versus ≥ 1%), histology (squamous vs non-squamous), and gender (male versus female). It is expected that among them, approximately 540 subjects with non-squamous histology approximately 210 subjects with squamous histology will be randomized.

Sample size justification for OS comparison among non-squamous subjects

The sample size is calculated to compare OS between nivolumab in combination with chemotherapy (Arm H) and platinum doublet chemotherapy (Arm I), among subjects with non-squamous histology at randomization as stratified, under a two-side 0.05 type I error with 90% power consideration. The number of events was estimated assuming an exponential distribution for OS in each arm.

Approximately 311 events (i.e., deaths), observed among the randomized non-squamous subjects, provides 90% power to detect a hazard ratio (HR) of 0.69 with an overall type 1 error of 0.05 (two-sided). The HR of 0.69 corresponds to a 44.9% increase in the median OS, assuming a median OS of 13.3 months for platinum doublet chemotherapy (Arm I) and 19.3 months for experimental treatment arms (Arm H) respectively. It is projected that an observed hazard ratio of 0.796 or less, which corresponds to a 3.4 months or greater improvement in median OS (13.3 mo vs. 16.7 mo),

would result in a statistically significant improvement in OS for the experimental arm at the final OS analysis.

One formal interim analysis of OS are is planned for this study, after observing approximately 230 events (74% of the targeted OS events for final analysis). The stopping boundaries at the interim and final analyses will be based on the actual number of OS events at the time of the analysis using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. If the interim analysis is performed exactly at 230 events and if the p-value is ≤ 0.018, then the OS among non-squamous subjects would be statistically significant per DMC. In the event that this interim analysis is not statistically significant, the nominal significance level for the final look of OS after 311events would then be 0.044 (adjusted for interim analysis).

Assuming a piecewise accrual rate and above stated OS distribution assumptions, it will approximately take 25 months from FPFV to observe the required number of OS events for the final OS analysis (9 months for accrual and 16 months for minimum follow up).

Table 8.1.2-1 summarizes the key parameters of the sample size justification for OS comparison among non-squamous subjects in the part 2 of the study.

Table 8.1.2-1: Sample Size Justification for Non-squamous Subjects in Part 2 of the Study

Primary Endpoint	**OS**
Primary analysis Comparison Population	Arm H and Arm I non-squamous subjects
Power (interim analysis/final analysis)	90% (67.5%/22.5%)
Alpha	0.05
Hypothesized Median PFS chemotherapy (arm I) vs. nivolumab + chemotherapy (arm H) (months)	13.3 vs 19.3
Hypothesized Hazard ratio	0.69
Accrual Duration (months)	9
Timing of final analysis(FA) from randomization of first subject (months)	25
Sample size for Arms H and I-non-squamous subjects	540
Expected number of events for	
OS interim analysis (74% events)	230
OS final analysis	311

Sample size justification for OS comparison among all randomized subjects

Comparison of OS among all randomized subjects is one of the key secondary objectives. Approximately 398 events (i.e., deaths), observed among all randomized subjects in part 2 provides 90% power to detect a hazard ratio (HR) of 0.72 with a type 1 error of 0.05 (two-sided). The HR of 0.72 corresponds to a 39% increase in the median OS, assuming a median OS of 13.3 months for platinum doublet chemotherapy (arm I) and 18.5 months for nivolumab in combination

with chemotherapy (Arm H) respectively. One interim analysis of OS among all randomized subjects is planned at time of interim analysis of primary analysis of OS among non-squamous subjects. This formal interim comparison of OS among all randomized subjects would be conducted in a hierarchical manner, i.e. if the formal primary comparison of OS among non-squamous subjects is statistically significant then the formal comparison of OS among all randomized subjects would be conducted. The stopping boundaries at the interim and final analyses will be based on the actual number of OS events at the time of the analysis using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. If the interim analysis is performed exactly at 338 events, the study could be stopped by the DMC for OS superiority if the p-value is ≤ 0.03.In the event that this interim analysis is not statistically significant, the nominal significance level for the final look of OS after 398 events would then be 0.042 (adjusted for interim analysis). If the interim analysis for OS among non-squamous subjects is not positive, then the interim analysis of OS among all randomized subjects would not be conducted. The final analysis of OS among non-squamous subjects under such an instance would be conducted after observing 311 OS events in the non-squamous population. The final analysis for all randomized subjects would be conducted at the time of final analysis for non-squamous subjects.

Assuming a piecewise accrual rate, it will approximately take 25 months (9 months for accrual and 16 months for follow-up) from the randomization of the first subject to observe the required number of events among subjects randomized to Arm H and I for final OS analysis.

Table 8.1.2-2 summarizes the key parameters of the sample size justification in the part 2 of the study.

Table 8.1.2-2: Sample Size Justification in Part 2 of the Study

Primary Endpoint	**OS**
Primary analysis Comparison population	Arm H and Arm I
Power (interim analysis /final analysis	90% (80%/10%)
Alpha	0.05
Hypothesized Median PFS chemotherapy (arm I) vs. nivolumab + chemotherapy (arm H) (months)	13.3 vs 18.5
Hypothesized Hazard ratio	0.72
Accrual Duration (months)	7.5
Timing of final analysis(FA) from randomization of first subject (months)	22
Sample size for Arms H and I	750
Expected number of events for	
OS interim analysis (85% events)	338
OS final analysis	398

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8.2 Populations for Analyses

8.2.1 Populations for PFS Analysis of high TMB subjects in Part 1

- **All Enrolled Subjects**: All subjects who signed an informed consent form and were registered into the IVRS of Part 1. This population will be used to for analysis of study conduct.
- **All Randomized Subjects:** All subjects who were randomized to any treatment arm in Part 1. This is the ITT population of Part 1 and is served as the reference for analyses of demography, protocol deviations, baseline characteristics, and efficacy among TMB high subjects.
- **TMB evaluable Subjects:** All randomized in Part 1 with baseline evaluable TMB. This population will be used for analysis of general concordance with the ITT population and distribution of TMB at baseline.
- **All Randomized Subjects with Baseline High TMB:** all randomized in Part 1 who had baseline high TMB as defined the following: for analysis of nivolumab in combination of ipilimumab (pooled Arms B and D) vs. platinum-doublet chemotherapy (pooled Arms C and F). This is the primary efficacy analysis population. For analysis of nivolumab (Arm A) vs. platinum-doublet chemotherapy (Arm C).
- **All Randomized Subjects with Baseline Low TMB:** all randomized in Part 1 who had baseline low TMB as defined the following: for analysis of nivolumab in combination of ipilimumab (pooled Arms B and D) vs. platinum-doublet chemotherapy (pooled Arms C and F); for analysis of nivolumab (Arm A) vs. platinum-doublet chemotherapy (Arm C). This is complement set of the primary efficacy population. Selected baseline, safety and efficacy analysis will be performed for this population.
- **All Response Evaluable Subjects:** all randomized subjects whose change in the sum of diameters of target lesions was assessed, i.e., target lesion measurements were made at baseline and at least one on-study tumor assessment. This population is used for analysis of tumor burden changes over the time in Part 1.
- **All Treated Subjects:** all randomized subjects who received at least one dose of any study medication in Part 1. This is the primary dataset for dosing and safety in Part 1.
- **Immunogenicity Subjects:** all nivolumab or ipilimumab treated subjects with available ADA data in Part 1.

8.2.2 Populations for Analysis at Interim/Final OS analysis in Part 1A

- **All Enrolled Subjects**: All subjects who signed an informed consent form and were registered into the IVRS of the individual substudies. Part 2 enrollment will begin after Part 1 enrollment has concluded. This population will be used to for analysis of study conduct for the individual substudy.

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- **All Randomized Subjects:** All subjects who were randomized to any treatment arm in the individual substudies. This is the dataset for analyses of demography, protocol deviations, baseline characteristics, and efficacy and outcome research in individual substudies.
- **All Randomized Subjects in Arm F who were Concurrently Randomized with Arm G:** all randomized subjects in Arm F who were concurrently randomized with Arm G post amendment 09. This is the analysis population of Arm F to be used for sensitivity analyses of efficacy (between Arm G and Arm F) in Part 1B.
- **All Response Evaluable Subjects:** randomized subjects whose change in the sum of diameters of target lesions was assessed, i.e., target lesion measurements were made at baseline and at least one on-study tumor assessment. This population is used for analysis of tumor burden changes over the time.
- **All Treated Subjects:** all randomized subjects who received at least one dose of any study medication in the individual substudies. This is the primary dataset for dosing and safety.
- **Immunogenicity Subjects:** all nivolumab or ipilimumab treated subjects with available ADA data.

8.2.3 Populations for Analysis in Part 2

- **All enrolled subjects**: all subjects who signed an informed consent form and were registered into the IVRS. Part 2 enrollment will begin after Part1 enrollment has concluded. This population will be used to for analysis of study conduct.
- **All randomized subjects (ITT population)**: all subjects who were randomized to any treatment arm. This is the dataset for analyses of demography, protocol deviations, baseline characteristics, and efficacy and outcome research in individual substudies.
- **All randomized subjects with non-squamous histology**: all subjects with non-squamous histology who were randomized to either treatment arm.
- **All Response evaluable subjects:** randomized subjects whose change in the sum of diameters of target lesions was assessed, i.e., target lesion measurements were made at baseline and at least one on-study tumor assessment. This population is used for analysis of tumor burden changes over the time.
- **All Treated Subjects:** all randomized subjects who received at least one dose of any study medication. This is the primary dataset for dosing and safety.
- **All Randomized Subjects with Baseline High TMB (≥ 10 mut/Mb)**: all randomized in Part 2 who had baseline high TMB.
- **Immunogenicity Subjects:** all treated subjects among nivolumab containing treatment group with available ADA data.

8.3 Endpoints

8.3.1 Primary Endpoints

In Part 1 the co-primary objectives will be measured by OS and PFS assessed by BICR. In Part 2 the primary endpoint is OS.

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OS is defined as the time between the date of randomization and the date of death due to any cause. OS will be censored on the last date a subject was known to be alive. OS will be followed continuously while subjects are on the study drug and every 3 months via in-person or phone contact after subjects discontinue the study drug.

PFS is defined as the time between the date of randomization and the first date of documented progression, as determined by BICR, or death due to any cause, whichever occurs first. Subjects who die without a reported progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subject who did not have any on study tumor assessments and did not die will be censored on their date of randomization. Subjects who had palliative local therapy or initiated anti-cancer therapy without a prior reported progression will be censored on the date of their last evaluable tumor assessment prior to the initiation of subsequent anti-cancer therapy or palliative local therapy. Tumor assessments are scheduled to be performed at week 6 (± 7 days) from first dose date, every 6 weeks until week 48 (± 7 days) and then every 12 weeks (± 7 days) until disease progression or treatment discontinuation, whichever occurs later.

8.3.2 Secondary Endpoints

8.3.2.1 OS and PFS

OS and PFS are also used to evaluate secondary objectives in Part 1 and Part 2. The definitions for OS and PFS are identical as described in Section 8.3.1

8.3.2.2 Objective Response Rate (ORR)

ORR is considered as a secondary endpoint for all individual substudies. ORR is defined as the number of subjects with a BOR of CR or PR divided by the number of randomized subjects for each treatment group. BOR is defined as the best response designation, recorded between the date of randomization and the date of objectively documented progression per RECIST 1.1 as determined by BICR or the date of initiation of palliative local therapy or the date of subsequent anti-cancer 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 study medication beyond progression, the BOR should be determined based on response designations recorded at the time of the initial RECIST 1.1 defined progression.

8.3.2.3 Time to Response and Duration of Response

Time to response and duration of response are secondary endpoints in all individual substudies to support ORR endpoint.

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

Duration of objective response (DOR) is defined as the time between the date of first confirmed response to the date of the first documented tumor progression (per RECIST 1.1) per BICR assessment, or death due to any cause, whichever occurs first. Subjects who neither progress nor

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die will be censored on the date of their last evaluable tumor assessment. Subjects who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last evaluable tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy. DOR will be evaluated for responders (i.e. subjects with confirmed CR or PR) only as assessed by BICR.

8.3.3 Exploratory Endpoints

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

Adverse event assessment and laboratory tests are performed at baseline, and continuously throughout the study at the beginning of each subsequent cycle.

The PK objective will be measured from serum concentration. Samples will be collected to characterize pharmacokinetics of nivolumab and to explore exposure-safety and exposure - efficacy relationships.

Disease-Related Symptom Deterioration Rate by week 12 is defined as the proportion of subjects who had 10 points or more increase from baseline in the LCSS Average Symptom Burden Index (ABSI) score at any time between baseline and Week 12. The time to deterioration in symptoms, is defined by the time to a clinically meaningful change (10 points or more) from baseline in the LCSS average symptom burden index (ASBI). A formal definition will be discussed in the statistical analysis plan.

The LCSS is a measure of disease-related symptoms and quality of life suited to use in patients suffering from lung cancer. It includes six items measuring loss of appetite, fatigue, coughing, shortness of breath, hemoptysis, and pain. Three additional items measure overall symptom burden, disease-related functional limitations, and quality of life. The questionnaire uses a 24 hour recall period, and responses for each item are captured using a 100-mm visual analog scale (VAS). Scores for individual items ranging from 0 (no symptomatology or highest quality of life) to 100 (worst symptomatology or quality of life) are derived by dividing the length of the line drawn from the lowest possible response to the patient's response by the length of the VAS and multiplying the resulting quotient by 100. An average symptom burden index (ASBI) score can be derived as the average of scores for the six symptom-related items with a clinically meaningful change in ASBI score being defined as 10 points. Accordingly, a meaningful deterioration in symptoms as measured by the ASBI is reflected in a mean post-baseline score change $\geq$ 10 points.

PFS after next line of treatment (PFS-2) is defined as the time from randomization to the date of investigator-defined documented second objective disease progression after second-line therapy or death due to any cause, whichever comes first. Clinical deterioration will not be considered as progression. A subject who neither progresses nor dies will be censored on the date of his/her last adequate tumor assessment or last follow-up for progression/subsequent therapy. A subject who does not have any post-baseline tumor assessments and who has not died will be censored on the date at which he/she was randomized.

Other exploratory endpoints are discussed in details in the statistical analysis plan.

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8.4 Statistical Analyses

Statistical analyses outlined in this section are applicable across endpoints and populations in general, unless otherwise specified. Analyses for primary endpoint will be performed at scheduled interim and final analyses. If the pre-specified superiority boundaries are crossed at the scheduled interim analyses and the corresponding substudy or substudies are unblinded, the secondary and exploratory endpoints will also be analyzed. Potential integrated analysis may be performed cross substudies depending on the availability of data at the time of analysis. Additional details will be provided in statistical analysis plan.

8.4.1 Demographics and Baseline Characteristics

Demographics and baseline laboratory results will be summarized by treatment arm as randomized using descriptive statistics for all randomized subjects in individual substudy.

8.4.2 Efficacy Analyses

8.4.2.1 Primary Endpoint Methods

8.4.2.1.1 Progression-free Survival in TMB High Subjects in Part 1

PFS per BICR assessment co-primary hypothesis testing for nivolumab in combination with ipilimumab (pooled Arms B and D) to platinum-doublet chemotherapy (pooled Arms C and F) in subjects with high baseline TMB regardless of PD-L1 expression level will be based on a unstratified log-rank test using a two-sided alpha 0.025. No PFS interim analysis is planned for this analysis population.

Hazard ratios (HR) of PFS (nivolumab in combination of ipilimumab vs. platinum doublet chemotherapy) and corresponding two-sided 97.5 % confidence intervals (CI) will be estimated using an unstratified Cox proportional hazard model, with treatment group as a single covariate.
PFS curves, PFS medians with 95% CIs, and PFS rates at 6, 12, 18, and 24 months with 95% CIs will be estimated by treatment group using Kaplan-Meier methodology.

8.4.2.1.2 Overall Survival in Part 1A

There are two scheduled OS analyses each for Part 1A: one OS interim analysis (IA) and one OS final analysis (FA).

1) OS co-primary hypothesis testing for nivolumab in combination of ipilimumab (Arm B) and platinum doublet chemotherapy (Arm C) with baseline PD-L1 expression ≥ 1% will be based on a two-sided stratified log-rank test stratified by histology.

The alpha spending allocated to the testing is based on the number of events at the time of interim analyses based on Lan-DeMets alpha spending function.
Hazard ratios (HR) of OS (Arm B vs. Arm C, Arm A vs. Arm C or Arm B vs. Arm A) and corresponding two-sided confidence intervals (CI) will be estimated using a stratified Cox proportional hazard model, with treatment group as a single covariate.

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OS curves, OS medians with 95% CIs, and OS rates at 6, 12, 18, 24, 36, and 48 months with 95% CIs will be estimated by treatment group using Kaplan-Meier methodology if follow-up requirement is met.

8.4.2.1.3 Overall Survival in Part 2

There are two scheduled OS analyses for non-squamous subjects randomized in Part 2: one OS interim analysis and one OS final analysis. OS primary hypothesis testing for nivolumab in combination with chemotherapy (Arm H) and chemotherapy (Arm I), among non-squamous subjects, will be based on a two-sided stratified log-rank test stratified by PD-L1 expression and gender. The alpha spending allocated to the testing is based on the number of events at the time of interim analyses based on Lan-DeMets alpha spending function.

Hazard ratios of OS (Arm H vs. Arm I) and corresponding two-sided 95% confidence intervals will be estimated using a Cox proportional hazard model, with treatment group as a single covariate stratified by histology, PD-L1 expression and gender. OS curves, OS medians with 95% CIs, and OS rates at 6, 12, 18, 24, 36, and 48 months with 95% CIs will be estimated by treatment group using Kaplan Meier methodology if follow-up requirement is met. Similar analysis would be conducted for comparison of OS among all randomized subjects, towards the secondary objective in Part 2.

8.4.2.2 Secondary Endpoint Methods

8.4.2.2.1 Hierarchical Testing Procedure

Hierarchical Testing Procedure (Part 1 TMB co-primary objective paradigm)

If the superiority of PFS per BICR assessment for the comparison between nivolumab in combination with ipilimumab (pooled Arms B and D) and platinum-doublet chemotherapy (pooled Arms C and F) among baseline high TMB subjects is demonstrated at a two sided type I error rate 0.025, a hierarchical hypothesis testing approach for the secondary endpoints will be used at the following order:

1) PFS per BICR assessment of nivolumab (Arm A) to platinum-doublet chemotherapy (Arm C) in subjects whose tumors have ≥ 1% PD-L1 expression and with baseline high tumor mutation burden. This comparison is based on a two-sided unstratified log-rank test.
2) OS of nivolumab in combination with ipilimumab (Arms B and D) to platinum-doublet chemotherapy (Arms C and F) in subjects with baseline high tumor mutation burden regardless PD-L1 expression level. This comparison is based on a two-sided unstratified log-rank test. This test will be performed if OS data are mature and Part 1A OS data are unblinded.
3) OS of nivolumab (Arm A) to platinum-doublet chemotherapy (Arm C) in subjects whose tumors have ≥ 1% PD-L1 expression and with baseline tumor mutation burden. This comparison is based on a two-sided unstratified log-rank test. This test will be performed if OS data are mature and Part 1A OS data are unblinded.

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The methodology used to analyze PFS and OS for the primary endpoint will also be used to analyze the secondary objectives in Part 1.

Hierarchical Testing Procedure (Part 1A OS co-primary objective paradigm)

If the superiority of OS is demonstrated for subjects in nivolumab in combination of ipilimumab (Arm B) and platinum doublet chemotherapy (Arm C) with baseline PD-L1 expression ≥ 1% at either interim analysis or final analysis, a hierarchical hypothesis testing approach for the secondary endpoints will be used at the following order to preserve the type I error rate at 0.025 in Part 1A. All the comparison will be performed under the same alpha level as used in the primary OS comparison.

1) PFS, based on BICR assessment, of nivolumab in combination with platinum-doublet chemotherapy (Arm G), to platinum-doublet chemotherapy (Arm F) in subjects whose tumors do not express PD-L1 (< 1%)
2) OS of nivolumab in combination with platinum-doublet chemotherapy (Arm G), to platinum-doublet chemotherapy (Arm F) in subjects whose tumors do not express PD-L1 (< 1%)
3) OS of nivolumab monotherapy (Arm A) to platinum-doublet chemotherapy (Arm C) in subjects whose tumors have ≥ 50% PD-L1 expression

Hierarchical Testing Procedure (Part 2 OS objective paradigm)

An overall hierarchical testing procedure[67] will be used to assess the secondary objective of comparing OS among all randomized subjects, if the primary comparison of OS among non-squamous subjects is statistically significant.

A separate group sequential spending function will be used to adjust for the overall Type I error at the interim and final analysis for each of the two formal comparisons of OS objectives (among non-squamous subjects and among all randomized subjects). The actual level of significance at which each objective is assessed will be determined based on the individual group sequential spending function and the amount of information spent at the time of the analysis. If the interim analysis for OS among non-squamous subjects is not positive, then the interim analysis of OS among all randomized subjects would not be conducted. The final analysis of OS among non-squamous subjects under such an instance would be conducted after observing 311 OS events in the non-squamous population. The final analysis for all randomized subjects would be conducted at the time of final analysis for non-squamous subjects. This procedure will ensure that the overall experiment-wise Type I error rate for the study is controlled at the 0.05 level.

The following are also secondary objectives but not part of the hierarchy:

- <u>In subjects with non-squamous histology</u>:
  - To compare the OS of nivolumab in combination with platinum-doublet chemotherapy (Arm H, among high baseline tumor mutation burden (≥ 10 mut/Mb subgroup
  - To compare the PFS, based on BICR assessment, of nivolumab in combination with platinum-doublet chemotherapy (Arm H), to platinum-doublet chemotherapy (Arm I)

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- To compare the ORR (BICR assessment) of nivolumab in combination with platinum doublet chemotherapy (Arm H), to platinum-doublet chemotherapy (Arm I)
- To evaluate efficacy (OS, PFS, and ORR) by PD-L1 expressing levels for nivolumab in combination with platinum-doublet chemotherapy (Arm H) and platinum-doublet chemotherapy (Arm I)
- To evaluate efficacy (OS, PFS, and ORR) by TMB levels for nivolumab in combination with platinum-doublet chemotherapy (Arm H) and platinum-doublet chemotherapy (Arm I)

- In all randomized subjects (ITT population):
  - In subjects with high baseline tumor mutation burden (≥ 10 mut/Mb): To compare the OS of nivolumab in combination with platinum-doublet chemotherapy (Arm H)
  - To compare the PFS, based on BICR assessment, of nivolumab in combination with platinum-doublet chemotherapy (Arm H), to platinum-doublet chemotherapy (Arm I)
  - To compare the ORR (BICR assessment) of nivolumab in combination with platinum-doublet chemotherapy (Arm H), to platinum-doublet chemotherapy (Arm I)
  - To evaluate efficacy (OS, PFS, and ORR) by PD-L1 expressing levels for nivolumab in combination with platinum-doublet chemotherapy (Arm H) and platinum-doublet chemotherapy (Arm I)
  - To evaluate efficacy (OS, PFS, and ORR) by TMB levels for nivolumab in combination with platinum-doublet chemotherapy (Arm H) and platinum-doublet chemotherapy (Arm I)

8.4.2.2.2 OS and PFS in Part 1and Part 2

For Part 1, methodology used to analyze OS and PFS as secondary endpoints will be very similar as that used to analyze OS and PFS as primary endpoint except the hierarchical testing procedure consideration.

In Part 2, OS comparison of nivolumab in combination with chemotherapy (Arm H) with platinum-doublet chemotherapy (Arm I) will be conducted among subjects with high baseline tumor mutation burden (≥ 10 mut/MB). Hazard ratios of OS (Arm H vs. Arm I) and corresponding two-sided 95% confidence intervals will be estimated using a Cox proportional hazard model, with treatment group as a single covariate. OS curves, OS medians with 95% CIs, and OS rates at 6, 12, 18, 24, 36, and 48 months with 95% CIs will be estimated using Kaplan-Meier methodology if follow-up requirement is met.

For Part 2, PFS comparison of nivolumab in combination with chemotherapy (Arm H) with platinum-doublet chemotherapy (Arm I) will be conducted, stratified by histology, PD-L1 expression and gender.

Hazard ratios of PFS (Arm H vs. Arm I) and corresponding two-sided 95% confidence intervals will be estimated using a Cox proportional hazard model, with treatment group as a single covariate, stratified by histology, PD-L1 expression and gender. PFS curves, PFS medians with 95% CIs, and PFS rates at 6, 12, 18, 24, 36, and 48 months with 95% CIs will be estimated using Kaplan-Meier methodology if follow-up requirement is met.

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Additional details will be provided in statistical analysis plan.

8.4.2.2.3 ORR in TMB high subjects of Part 1

BICR-determined ORR among high TMB subjects (for nivolumab in combination of ipilimumab related analysis and for nivolumab monotherapy related analysis) in Part 1 will be estimated and its corresponding 95% exact two-sided CIs will be calculated using the Clopper Pearson method. The unweighted differences in ORR between the two treatment groups and corresponding 95% two-sided CI using the method of Newcombe will be provided. BOR as determined by BICR will be summarized by response category for each treatment group.

8.4.2.2.4 ORR in Part 2

BICR-determined ORR in Part 2 will be estimated and its corresponding 95% exact two-sided CIs will be calculated using the Clopper Pearson method. The unweighted differences in ORR between the two treatment groups and corresponding 95% two-sided CI using the method of Newcombe will be provided. BOR as determined by BICR will be summarized by response category for each treatment group

8.4.2.2.5 Time to Response and Duration of Response

Time to response and duration of response are secondary/exploratory endpoints in all substudies (Part 1A, Part 1B and Part 2). Summary statistics of time to objective response will be provided for each treatment group for subjects who achieve PR or CR for individual substudy separately.

Duration of response in each treatment group will be estimated using KM product-limit method for subjects who achieve PR or CR for individual substudy separately. Median values along with two-sided 95% CI will be calculated. Summary statistics will be computed constructed based on a log-log transformed CI for the survivor function. Additional sensitivity analysis for DOR will be specified in the SAP.

8.4.3 Exploratory Analyses

PFS-2 is defined as the time from randomization to the date of investigator-defined documented second objective disease progression after second-line therapy or death due to any cause, whichever comes first. Clinical deterioration will not be considered as progression. A subject who neither progresses nor dies will be censored on the date of his/her last adequate tumor assessment or last follow-up for progression/subsequent therapy. A subject who does not have any post-baseline tumor assessments and who has not died will be censored on the date at which he/she was randomized.

8.4.4 Safety Analyses

Safety analysis will be performed in all treated subjects for each substudy. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 by treatment group. All on-study AEs, drug-related AEs, SAEs and drug-related SAEs will be tabulated using worst grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term. On-study lab parameters including hematology,

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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 and comparative analysis between treatment arms of the incidence of overall IMAEs (by preferred term) and serious IMAEs will be performed. A descriptive analysis of IMAEs including time-to-onset, severity, duration, action taken with the study drug, dosing delays of the study drug, corticosteroid details, re-challenge information and outcome of the AE are individually characterized:

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

8.4.5 Pharmacokinetic Analyses

The nivolumab concentration data obtained in this study may be combined with data from other studies in the clinical development programs to develop or refine a population PK model. These models may be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of nivolumab and ipilimumab to determine measures of individual exposure. In addition, model determined exposures of nivolumab alone, in combination with ipilimumab or nivolumab in combination with platinum-doublet chemotherapy may be used for exposure-response analyses with efficacy and safety measures in combination. Results of population PK and exposure-response analyses will be reported separately.

[redacted]

8.4.7 Outcomes Research Analyses

The outcomes research analyses will be performed for the target populations of interest at the time of final analysis of OS or PFS. Both the LCSS and EQ 5D questionnaire completion rates, defined as the proportion of questionnaires actually received out of the expected number (i.e., the number of subjects still on treatment in follow-up), will be calculated and summarized at each assessment point.

The disease-related symptom deterioration rate by week 12 and its corresponding 95% exact CI will also be calculated by Clopper-Pearson method for the target population of interest in each treatment group. The time to deterioration in symptoms, as defined by the changes from baseline in the LCSS average symptom burden index (ASBI) will be calculated using Kaplan-Meier methods. The LCSS ASBI score and the within-patient change from baseline at each LCSS assessment point will be summarized using descriptive statistics (N, mean, median, SD, 25th and 75th percentiles, 95% CI) for the target population of interest in each treatment group.

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The EQ-5D will be used to assess the subjects' overall health status. The EQ-5D has two components -- the EQ-5D descriptive system and the EQ-5D visual analogue scale (EQ-5D VAS). The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, sever problems. The EQ-5D Utility Index will be computed from the EQ-5D descriptive systems responses. The EQ-5D VAS records the subjects' self-rated health state on a 100-point vertical, visual analogue scale (0=worst imaginable health state, 100=best imaginable health state). Subjects' overall health status according to both the EQ-5D VAS and the EQ-5D Utility Index and as well as within-patient changes from baseline in each measure at each assessment time point will be summarized using descriptive statistics (N, mean, median, SD, 25th and 75th percentiles, 95% CI) for the target population of interest in each treatment group. In addition, the proportion of subjects reporting each of the problem levels (no problems, some problems, extreme problems) for each of the 5 EQ-5D dimensions at each assessment time point will be summarized by level of problem and for the target population of interest in each treatment group. Percentages will be based on number of subjects responding at each assessment time point.

8.4.8 Other Analyses

Methodology for exploratory analyses including immunogenicity is described in the statistical analysis plan.

8.5 Interim Analyses

8.5.1 Interim Analysis of OS in Part 1A

In Part 1A, one formal interim analysis for OS is planned at 70% of total events needed for the final analysis, i.e. 387 events are needed for Arms B and C for the interim analyses of OS. This formal comparison of OS, by DMC, will allow for early stopping for superiority. Lan-DeMets alpha spending function with O'Brien and Fleming type of boundary will be used. The stopping boundary will depend on the actual number of deaths at the time of the interim analysis. However, for Part 1A if the analysis were performed exactly at 70% of total events, the nominal significance level for OS superiority will be 0.006. An independent statistician external to BMS will perform the analysis.

If Part 1A continues beyond the interim analyses the nominal significance level for the final analysis of OS after target events (553) would be 0.023. All events in the database at the time of the lock will be used. If number of final events exceeds the number specified per protocol for each individual substudy, final boundary will not be recalculated using updated information fraction at interim. In addition to the formal planned interim analyses for OS, the DMC will have access to periodic unblinded interim reports of efficacy and safety to allow a risk/benefit assessment during periodic safety reviews. However, no formal test will be performed and the study will not be stopped for the superiority during safety reviews. Additional details will be included in the DMC charter.

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8.5.2 Interim Analysis of OS in Part 2

Interim analysis of OS among non-squamous subjects

One formal interim analysis of OS is planned for this study, after observing approximately 230 events (74% of the targeted OS events for final analysis). The stopping boundaries at the interim and final analyses will be based on the actual number of OS events at the time of the analysis using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. If the interim analysis is performed exactly at 230 events and if the p-value is ≤ 0.018, then the OS among non-squamous subjects would be statistically significant per DMC. In the event that this interim analysis is not statistically significant, the nominal significance level for the final look of OS after 311 events would then be 0.044 (adjusted for interim analysis). If the formal interim analysis for OS among non-squamous subjects is positive at interim, and the interim analysis is also positive at that point in time, the DMC can recommend to stop the study. If the formal interim analysis of OS among non-squamous subjects is statistically significant and the formal comparison of OS among all randomized subjects is not statistically significant at interim then the study will continue as planned for the final comparison of OS among all randomized subjects. The final analysis of OS among all randomized subjects under such an instance would be conducted after observing 398 OS events in the ITT population.

If the interim analysis for OS among non-squamous subjects is not positive, then the interim analysis of OS among all randomized subjects would not be conducted. The final analysis of OS among non-squamous subjects under such an instance would be conducted after observing 311 OS events in the non-squamous population. The final analysis for all randomized subjects would be conducted at the time of final analysis for non-squamous subjects.

Interim analysis of OS among all randomized subjects

If the formal interim analysis of OS among non-squamous subjects is statistically significant then a formal interim analysis of OS among all randomized subjects would be conducted. The stopping boundaries at the interim and final analyses will be based on the actual number of OS events at the time of the analysis using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. If this interim analysis is performed exactly at 341 events and if the p-value is ≤ 0.03, then the OS among all randomized subjects would be statistically significant per DMC and the study could be stopped. The nominal significance level for the final look of OS after 398 events would then be 0.042 (adjusted for interim analysis). The DMC can recommend stopping the study only if both the comparisons of OS among non-squamous subjects and all randomized subjects are statistically significant at the time of interim analysis.

If the interim analysis for OS among non-squamous subjects is not positive, then the interim analysis of OS among all randomized subjects would not be conducted. The final analysis of OS among non-squamous subjects under such an instance would be conducted after observing 311 OS events in the non-squamous population. The final analysis for all randomized subjects would be conducted at the time of final analysis for non-squamous subjects.

All events in the database at the time of the lock will be used. If number of final events exceeds the number specified per protocol for each individual substudy, final boundary will not be

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recalculated using updated information fraction at interim. In addition to the formal planned interim analyses for OS, the DMC will have access to periodic unblinded interim reports of efficacy and safety to allow a risk/benefit assessment during periodic safety reviews. However, no formal test will be performed and the study will not be stopped for the superiority during safety reviews. Additional details will be included in the DMC charter.

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.

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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 (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., 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 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

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- amount transferred to another area/site for dispensing or storage
- nonstudy disposition (e.g., lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to BMS
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

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

9.2.3 Case Report Forms

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

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

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

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

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

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- Subject recruitment (e.g., 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 require approval by BMS prior to publication or presentation and must adhere to BMS's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to BMS at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. BMS shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

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10 GLOSSARY OF TERMS

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

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11 LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANC	absolute neutrophil count
AIDS	acquired immunodeficiency syndrome
aPTT	activated partial thromboplastin time
AE	AE
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AT	Aminotransaminases
AUC	area under the concentration-time curve
β-HCG	beta-human chorionic gonadotrophin
BID, bid	bis in die, twice daily
BICR	blinded independent central review
BMI	body mass index
BMS	Bristol-Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
C	Celsius
Ca++	Calcium
Cavg	average concentration
Cavgss	average concentration at steady state
Cminss	average trough concentration at steady state
Cmaxss	average peak concentration at steady state
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
C1-	Chloride
CLcr	creatinine clearance

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Term	Definition
Cm	Centimeter
CNS	Central nervous system
CRC	Clinical Research Center
CRF	Case Report Form, paper or electronic
CTLA-4	cytotoxic t lymphocyte-associated antigen 4
CYP	cytochrome p-450
D/C	Discontinue
dL	Deciliter
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEG	Electroencephalogram
E.g.	exempli gratia (for example)
ESR	Expedited Safety Report
FDA	Food and Drug Administration
[redacted]	[redacted]
FSH	follicle stimulating hormone
G	Gram
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GFR	glomerular filtration rate
H	Hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCO3-	Bicarbonate
HIV	Human Immunodeficiency Virus
HR	heart rate
HRQol	health related quality of life

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Term	Definition
HRT	hormone replacement therapy
ICD	International Classification of Diseases
ICF	informed consent form
ICH	International Conference on Harmonisation
I.e.	id est (that is)
IEC	Independent Ethics Committee
IMP	investigational medicinal products
IMAE	Immune-mediated adverse events
IND	Investigational New Drug Exemption
IRB	Institutional Review Board
IU	International Unit
IU/L	international unit per liter
IU/mL	international unit per milliliter
IVRS	interactive voice response system
IV	Intravenous
K3EDTA	potassium ethylenediaminetetraacetic acid
K+	Potassium
kD	Kilodalton
Kg	Kilogram
KM	kaplan-meier
L	Liter
LCSS	lung cancer symptom scale
LDH	lactate dehydrogenase
mAB	monoclonal antibody
Mg	Milligram
Mg++	Magnesium
[redacted]	
Min	Minute
mL	Milliliter
mmHg	millimeters of mercury

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Term	Definition
MTD	maximum tolerated dose
mWHO	modified World Health Organization
µg	Microgram
N	number of subjects or observations
Na+	Sodium
N/A	not applicable
NE	not evaluable
Ng	Nanogram
NIMP	non-investigational medicinal products
NSAID	nonsteroidal anti-inflammatory drug
ORR	overall response rate
OS	overall survival
PD	Pharmacodynamics
PD	progressive disease
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PFS	progression-free survival
PR	partial response
PK	Pharmacokinetics
PO	per os (by mouth route of administration)
PT	prothrombin time
PTT	partial thromboplastin time
QC	quality control
QD, qd	quaque die, once daily
RCC	renal cell carcinoma
RECIST 1.1	response evaluation criteria in solid tumors version 1.1
RBC	red blood cell
SAE	serious adverse event
SD	standard deviation

Term	Definition
SD	stable disease
SOP	Standard Operating Procedures
Subj	Subject
T	Temperature
T	Time
TAO	Trial Access Online, the BMS implementation of an EDC capability
T-HALF	Half life
TID, tid	ter in die, three times a day
[redacted]	[redacted]
TSH	thyroid stimulating hormone
Tmax, TMAX	time of maximum observed concentration
TMB	tumor mutation burden
ULN	upper limit of normal
VAS	visual analog scale
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential

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12 REFERENCES

REFERENCES FOR THE USE OF CONDOMS WITH SPERMICIDE.

Kestelman P. et. al., Efficacy of the Simultaneous Use of Condoms and Spermicides Family Planning Perspectives. Vol 23 (5); October 1991.

Gabbay MB, Thomas J, Gibbs A, Hold P. A Randomized Crossover Trial of The Impact of Additional Spermicide on Condom Failure Rates. Sex Transm Dis 2008; 35: 862-8.Bar

[1] Jemal A, Bray F, Center MM. et al. Global Cancer Statistics CA Cancer J Clin 2011; 61:69–90.

[2] NCCN Clinical Practice Guidelines in Oncology. Non-small cell lung cancer. v.3.2014. www.nccn.org.

[3] Mellman I, Coukos G & Dranoff G. Cancer immunotherapy comes of age. Nature 2011 Dec 22; 29 4 8 0:480-89.

[4] Brahmer JR, Drake CG, Wollner I, et al. Phase I Study of Single-Agent Anti–Programmed Death-1 (MDX-1106) in Refractory Solid Tumors: Safety, Clinical Activity, Pharmacodynamics, and Immunologic Correlates. J Clin Oncol 2010; 28:3167-3175.

[5] Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer. N Engl J Med 2015; 373:123-35.

[6] Rizvi NA, Mazières J, Planchard D, et al. Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. Lancet Oncol 2015; Published online February 20, 2015 http://dx.doi.org/10.1016/S1470-2045 (15)70054-9.

[7] Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer. N Engl J Med 2015; 373:1627-39.

[8] Socinski M, Creelan B, Horn L, et al. CheckMate 026: A Phase 3 Trial of Nivolumab vs Investigator's Choice (IC) of Platinum-Based Doublet Chemotherapy (PT-DC) as First-Line Therapy for Stage IV/Recurrent Programmed Death Ligand 1 (PD-L1) − Positive NSCLC. Ann Oncol 2016: 27(S): Abstract LBA7_PR.

[9] Amos S M., Duong CPM, Westwood JA, et al. Autoimmunity associated with immunotherapy of cancer. Blood 2011; 118:499-509.

[10] Sznol M, Kluger HM, Callahan MK, et al. J Clin Oncol 32:5s (suppl; abstrLBA 9003).

[11] Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med 2015; 372:2006-2017.

[12] Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer (supplemental appendix). N Engl J Med 2015; 373:123-35.

Approved v8.0 930088451 8.0

[13] Fehrenbacher L, Spiro A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet 2016: 387:837-46.

[14] Rizvi NA, Hellmann MD, Synyder, A, et al. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science 2015;348:124–8.

[15] Kowanetz M et al. Tumor mutation burden (TMB) is associated with improved efficacy of atezolizumab in 1L and 2L+ NSCLC patients. Oral presentation at WCLC 2016.

[16] Peters S, Creelan B, Hellmann MD, et al. Impact of tumor mutation burden on the efficacy of first-line nivolumab in stage IV or recurrent non-small cell lung cancer: an exploratory analysis of CheckMate 026. Oral presentation at the Annual Meeting of the American Association of Cancer Research; April 1-5, 2017; Washington, DC, USA.

[17] Curran MA, Montalvo W, Yagita H, et al. PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. PNAS 2010; 107: 4275-80.

[18] Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus ipilimumab in advanced melanoma. New Engl J Med 2013; 369: 122-33.

[19] Ipilimumab (BMS-734016) Investigator Brochure, version 17, 2014.

[20] Scagliotti GV, Parikh P, Von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced stage non-small cell lung cancer. J Clin Oncol 2008; 26: 3543-51.

[21] Azzoli CG, Baker S, Temin S, et al. American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non-Small Cell Lung Cancer. J Clin Oncol 2009; 27: 6251-66.

[22] Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol. 2016 Oct 10. pii: S1470-2045(16)30498-3. doi: 10.1016/S1470-2045(16)30498-3.

[23] Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009; 15:7412-20.

[24] Hellmann MD, Rizvi NA, Goldman JW, Gettinger SN, et al. Nivolumab plus ipilimumab first-line in advanced non-small-cell lung cancer: results of an open-label, phase 1, multicohort study (CheckMate 012). Lancet Oncol Manuscript submittedfor publication.

[25] Schadendorf D. Efficacy and quality of life outcomes in patients with advanced melanoma (MEL) who discontinued treatment with nivolumab (NIVO) plus ipilimumab (IPI) due to toxicity in a phase III trial (CheckMate 067). 2016 Annual Meeting of the European Association of Dermato-Oncology; August 31-September 3, 2016; Vienna, Austria.

[26] Robert C, Schachter J, Long GV, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med 2015; 372:2521-32.

[27] Schadendorf D, Hodi FS, Robert C, Weber JS, et al. Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma. J Clin Oncol 2015; 33: 1889-94.

[28] Spigel DR, McLeod M, Hussein MA. Randomized results of fixed-duration (1-yr) vs continuous nivolumab in patients (pts) with advanced non-small cell lung cancer (NSCLC). Oral presentation at ESMO 2017, Abstract 1297O.

[29] Brahmer J, Horn L, Jackman D, et al. Five-year follow-up from the CA209-003 study of nivolumab in previously treated advanced non-small cell lung cancer: clinical characteristics of long-term survivors. Oral presentation presented at: American Association for Cancer Research (AACR) Annual Meeting; April 1-5, 2017; Washington, DC, USA.

[30] Felipe E, Gettinger S, Burgio MA, et al. Three-year follow-up from CheckMate 017/057: Nivolumab versus docetaxel in patients with previously treated advanced non-small cell lung cancer (NSCLC). Poster presentation at ESMO 2017. Abstract 1301PD.

[31] Eberhard, DA, Johnson BE, Amler LC, et al. Mutations in the epidermal growth factor receptor and in KRAS are predictive and prognostic indicators in patients with non-small-cell lung cancer treated with chemotherapy alone and in combination with erlotinib. J Clin Oncol 2005; 2: 5900-5909.

i) [32] Mok TS, Wu Y, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009; 361-947-57.

[33] Shaw AT, Varghese AM, Solomon FJ, et al. Pemetrexed-based chemotherapy in patients with advanced, ALK-positive non-small cell lung cancer. Annals of Oncology 2013; 24: 59-66.

[34] Carbone DP, Reck M, Paz-Ares L, et al. First-Line Nivolumab in Stage IV or Recurrent Non–Small-Cell Lung Cancer. N Engl J Med 2017; 376:2415-26.

[35] Gandhi L, Rodriguez-Abreu D, Gadgeel S, Estaban E, et al. Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer. N Engl J Med 2018; 378: 2078-92.

[36] Socinski MA, Jotte RM, Cappuzzo F, Orlandi F, et al. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. N Engl J Med 2018; 378:2288-2301.

[37] Kowanetz M, Zou W, Shames DS, et al. Tumor mutation burden (TMB) is associated with improved efficacy of atezolizumab in 1L and 2L+ NSCLC patients. Oral presentation at: The 17th Annual World Conference on Lung Cancer; December 4-7, 2016; Vienna, Austria.

[38] Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer. N Eng J Med 601 2016; 375:1823-33.

[39] Pardoll DM, The blockade of immune checkpoints in cancer immunotherapy. Nature 2012; 12:252-64.

[40] Zitvogel L, Tesniere A, Kroemer G. Cancer despite immunosurveillance: immunoselection and immunosubversion. Nat Rev Immunol 2006; 6:715-27.

Approved v8.0 930088451 8.0

[41] Dunn GP, Bruce AT, Ikeda H, et al. Cancer immunoediting: from immunosurveillance to tumor escape. Nat Immunol 2002; 3:991-8.

[42] Horne ZD, Jack R, Gray ZT, et al. Increased levels of tumor-infiltrating lymphocytes are associated with improved recurrence-free survival in stage 1A non-small-cell lung cancer. J Surg Res. 2011; 171:1-5.

[43] Al-Shibli KI, Donnem T, Al-Saad S, et al. Prognostic effect of epithelial and stromal lymphocyte infiltration in non-small cell lung cancer. Clin Cancer Res 2008; 14:5220-7.

[44] Ruffini E, Asioli S, Filosso PL, et al. Clinical significance of tumor-infiltrating lymphocytes in lung neoplasms. Ann Thorac Surg 2009; 87:365-72.

[45] Greenwald RJ, Freeman GH, Sharpe AH. The B7 family revisited. Annu Rev Immunol 2004; 23:515-48.

[46] Zhang Y, Huang S, Gong D, et al. Programmed death-1 upregulation is correlated with dysfunction of tumor-infiltrating CD8+ T lymphocytes in human non-small cell lung cancer. Cell and Mol Immunol 2010; 7:389-95.

[47] Sharpe AH, Wherry EJ, Ahmed R, et al. The function of programmed cell death 1 and its ligands in regulating autoimmunity and infection. Nature Immunol 2007; 8:237-45.

[48] Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Eng J Med 2012; 366: 2443-54.

[49] Alegre ML, Noel PJ, Eisfelder BJ, et al. Regulation of surface and intracellular expression of CTLA4 on mouse T cells. J Immunol 1996; 157:4762-70.

[50] Postow MA, Harding J, Wolchok JD. Targeting immune checkpoints: Releasing the restraints on anti-tumor immunity for patients with melanoma. Cancer J 2012; 18:153-159.

[51] Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 20/5/2014.

[52] Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) Research Data (1973-2011), National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2014, based on the November 2013 submission. Non-Small Cell Cancer of the Lung and Bronchus (Invasive). 5-Year Relative and Period Survival by Race, Sex, Diagnosis Year, Age and Stage at Diagnosis.

[53] Paz-Ares LG, De Marinis F, Dediu M, et al. PARAMOUNT: Final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small cell lung cancer. J Clin Oncol 2013.

54 Belani CP, Ramalingam S, Perry MC, et al. Randomized, phase III study of weekly paclitaxel in combination with carboplatin versus standard every-3-weeks administration of carboplatin and paclitaxel for patients with previously untreated advanced non-small-cell lung cancer. J Clin Oncol 2008; 26: 468-73.

55 Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small cell lung cancer. N Eng J Med 2006; 355: 2542-50.

56 Patel JD, Socinski MA, Garon EB, et al. PointBreak: A randomized phase III study of pemetrexed plus carboplatin and bevacizumab followed by maintenance pemetrexed and bevacizumab versus paclitaxel plus carboplatin and bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non-small cell lung cancer. J Clin Oncol 2013; 34: 4349-57.

57 Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomized phase 3 trial. Lancet Oncol 2012; 13:239-46.

58 Tamiya T, Tamiya M, Kanazu M, Hirooks A, et al. Dose escalation study of carboplatin-pemetrexed followed by maintenance pemetrexed for elderly patients with advanced nonsquamous nonsmall-cell lung cancer. Ann Oncol 2012; 24:980-985.

59 Gronberg BH, Bremnes RM, Flotten O, et al. Phase II study by the Norwegian lung cancer study group: pemetrexed plus carboplatin compared with gemcitabine plus carboplatin as first-line chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol 2009; 27:3217-24.

60 Nivolumab (BMS-936558) Investigator Brochure, version 13, 2014.

61 Goldstraw P, Crowley J, Chansky K, Giroux DJ, et al. The IASLC Lung Cancer Staging Project: Proposals for the Revision of the TNM Stage Groupings in the Forthcoming (Seventh) Edition of the TNM Classification of Malignant Tumours. J Thorac Oncol 2007; 2:706-714.

62 Mandrekar SJ, Sargent DJ. Clinical trial designs for predictive biomarker validation: theoretical considerations and practical challenges. J Clin Oncol 2009; 27:4027-4034.

63 Cook MB, McGlynn KA, Devesa SS, Freedman ND, Anderson WF. Sex disparities in cancer mortality and survival. Cancer Epidemiol Biomarkers Prev 2011; 20:1629-37.

[redacted]

[67] Glimm E, Maurer W, Bretz F, et. al. Hierarchical testing of multiple endpoints in group-sequential trials. Statistics in Medicine. 2010; 29: 219-228.

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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

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

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APPENDIX 2 MANAGEMENT ALGORITHMS FOR IMMUNO-ONCOLOGY AGENTS

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

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

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

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

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

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GI Adverse Event Management Algorithm

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

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

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

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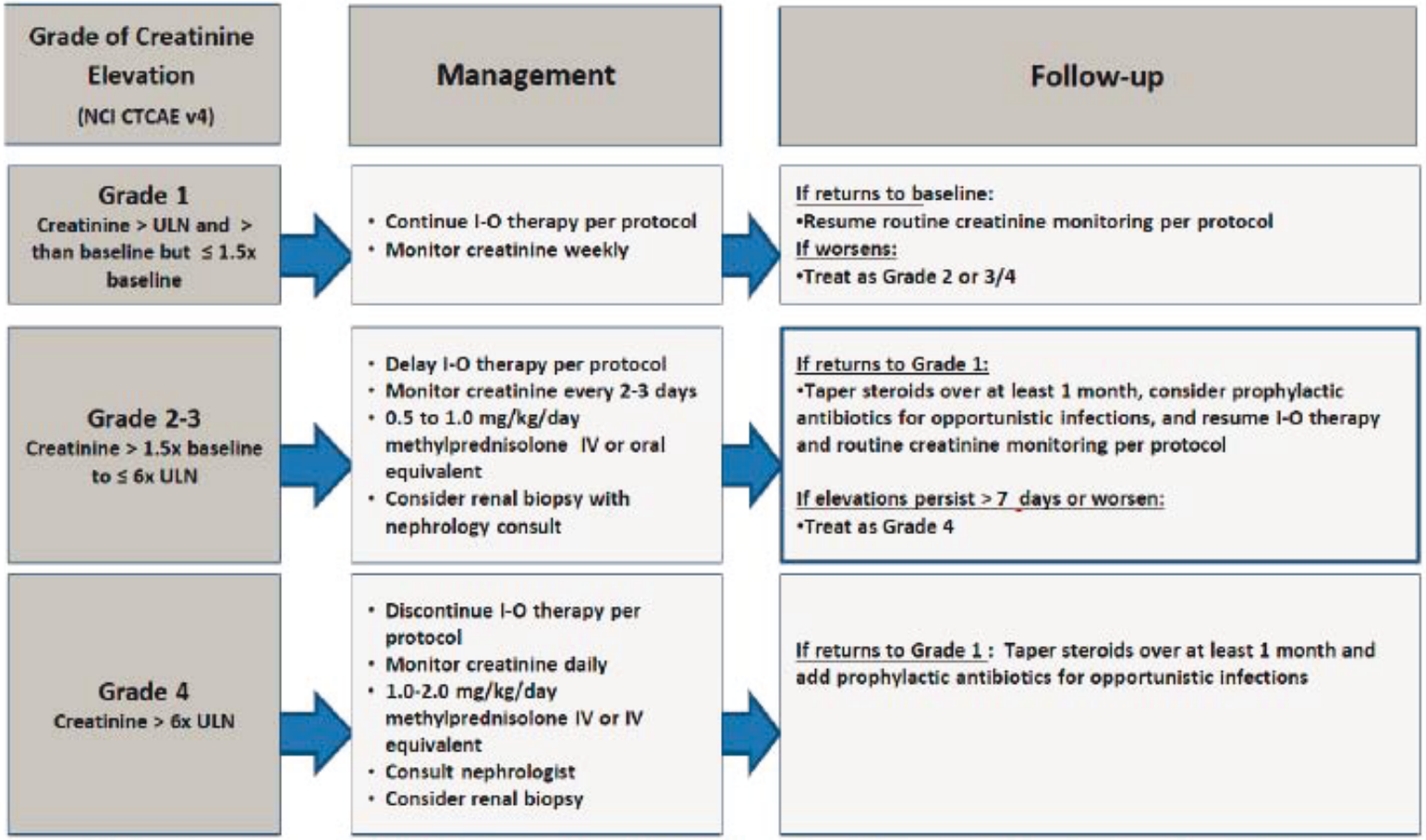
Renal Adverse Event Management Algorithm

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



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

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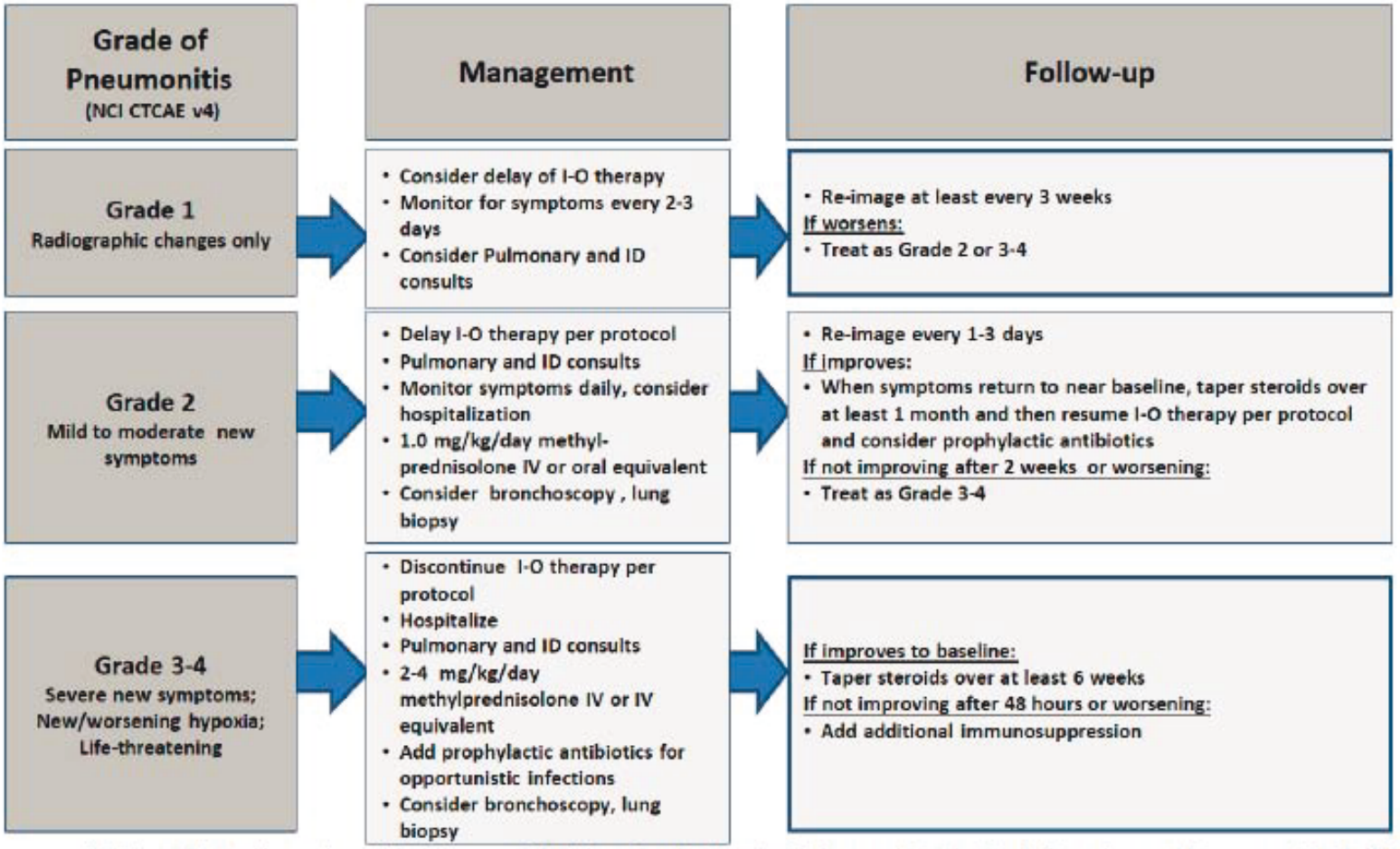
Pulmonary Adverse Event Management Algorithm

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



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

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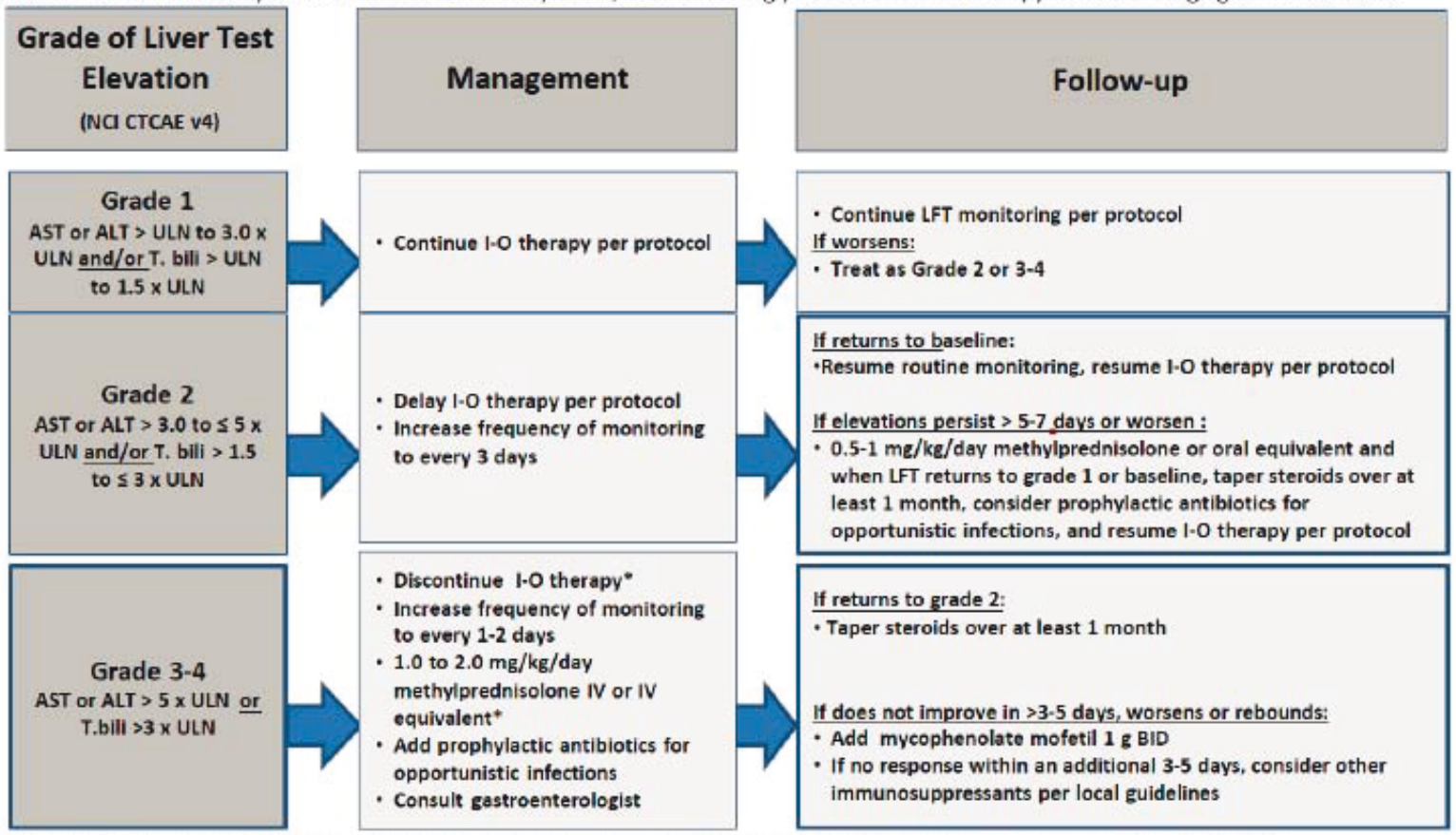
Hepatic Adverse Event Management Algorithm

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



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

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

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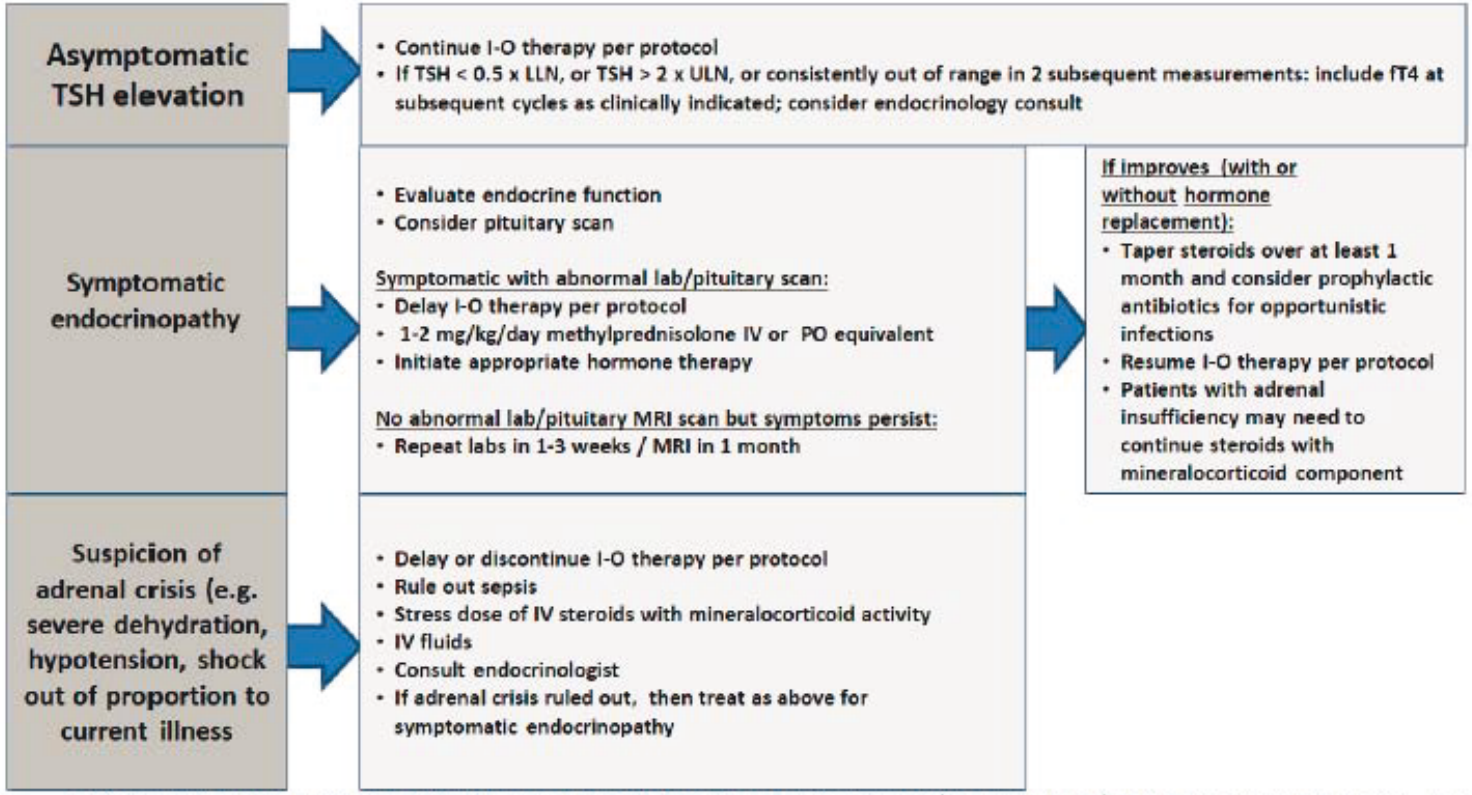
Endocrinopathy Adverse Event Management Algorithm

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



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

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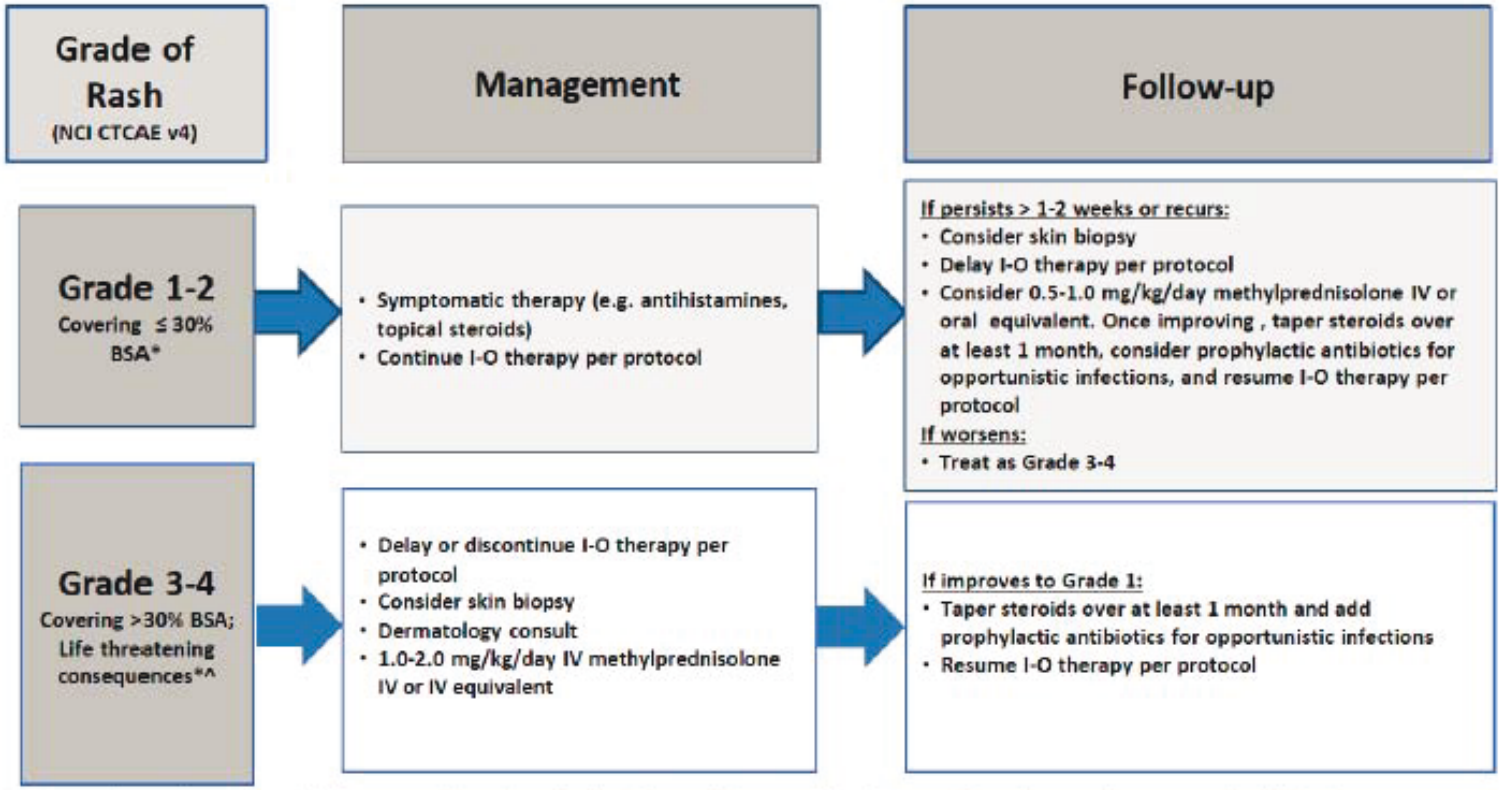
Skin Adverse Event Management Algorithm

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



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

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

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

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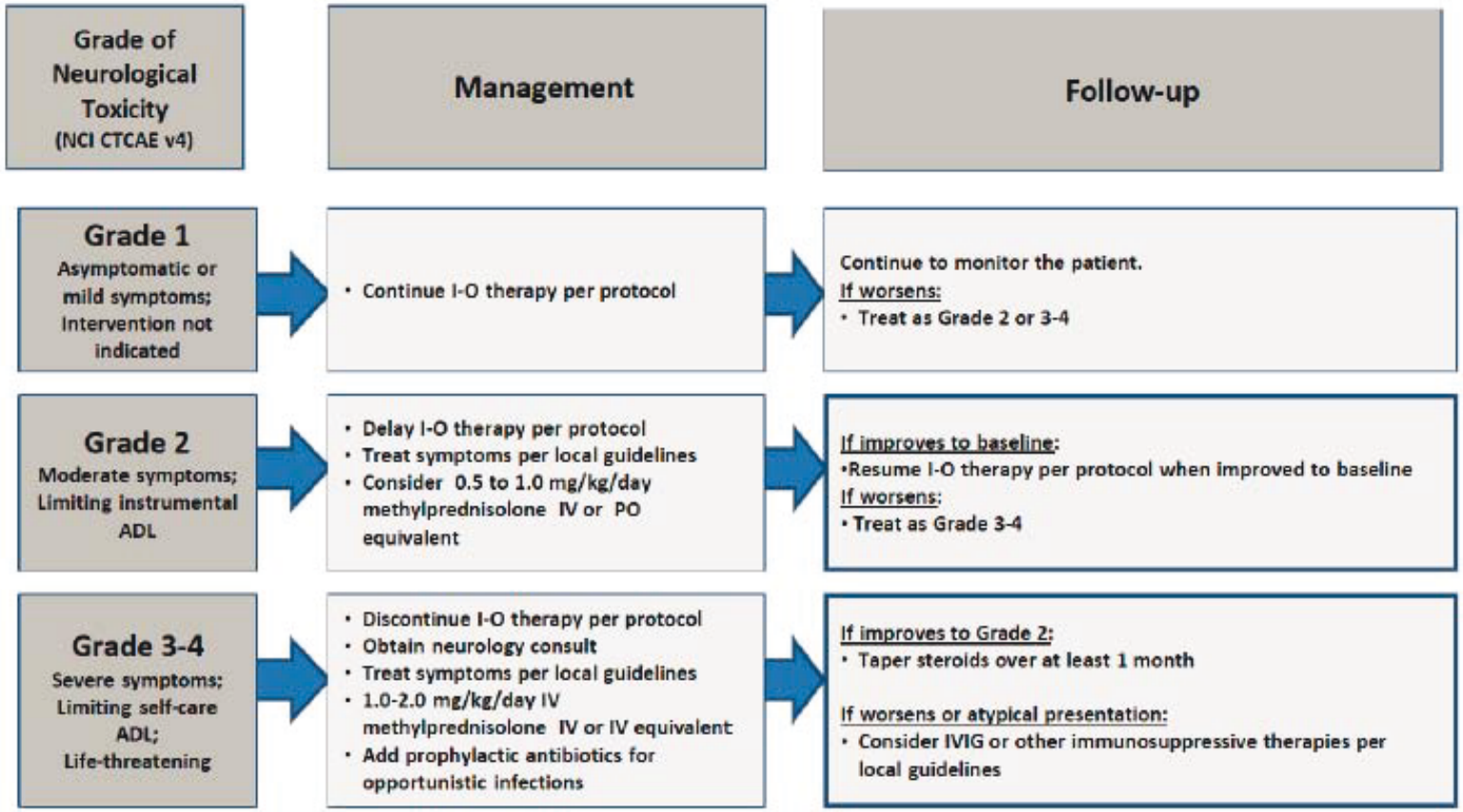
Neurological Adverse Event Management Algorithm

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



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

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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.

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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.

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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'.

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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

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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

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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.

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3.3.3 Best Overall Response

Best response determination of complete or partial response requires confirmation: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point of ≥ 4 weeks later. In this circumstance, the best overall response can be interpreted as in Table 3.3.3-1.

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

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

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

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

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

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

3.3.4 Confirmation Scans

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

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

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