Protocol for

Official Title of Study

A Dose Frequency Optimization, Phase IIIB/IV Trial of Nivolumab 240 mg Every 2 Weeks vs Nivolumab 480 mg Every 4 Weeks in Subjects with Advanced or Metastatic Non-small Cell Lung Cancer who Received Up to 12 Months of Nivolumab at 3 mg/kg or 240 mg Every 2 Weeks

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Clinical Protocol CA209384

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Revised Protocol 05

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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.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 05	26-Jun-2018	• Reduced sample size and modified primary endpoint from non-inferiority to one-sided confidence interval around the differences of PFS rates • Modified follow-up for overall survival for 3 years • Added rationale for maximum treatment duration with nivolumab of 2 years
Revised Protocol 04	09-Feb-2018	• Included additional language for nivolumab program level updates • Added information for interim analysis
Administrative Letter 02	09-Aug-2017	Updating study personnel
Administrative Letter 01	10-Jan-2017	Updating study personnel
Revised Protocol 03	12-Aug-2016	Incorporates Amendment 04
Amendment 04	12-Aug-2016	• To change the pre-study nivolumab requirement • Add a small increase to the sample size • Add immunogenicity as an endpoint • Make small changes to the laboratory and tumor assessments and duration of contraception use to align the protocol with updates to the nivolumab clinical development program.
Revised Protocol 02	12-Feb-2016	Incorporates Amendment 02
Amendment 02	12-Feb-2016	Change the Human Immunodeficiency Virus criterion to reflect the language that is used across the nivolumab clinical development program and adjusted the frequency of magnetic resonance imaging scans in those with a history of brain metastasis to align with study assessments.
Revised Protocol 01	11-Dec-2015	Incorporates Amendment 01
Amendment 01	11-Dec-2015	• Allows enrollment of subjects who are ineligible for or refuse chemotherapy in the first-line advanced non-small cell lung cancer setting • Allows use of flat dose in the pre-study period and during the investigational period. • Added HIV testing as a screening test
Original Protocol	03-Nov-2015	Not applicable

OVERALL RATIONALE FOR THE REVISED PROTOCOL 05

With the recent approval for new dose regimens including those used in this study and increasing use of immunotherapy in earlier lines of treatment, enrollment into the study has slowed. As full enrollment may not be achieved, enrollment was stopped and sample size was reduced with modified endpoint analyses and follow-up.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 05

Section Number & Title	Description of Change	Brief Rationale
Study schematic, Objectives, Section 1.3.2 Secondary Objectives, Section 1.4.1 Efficacy of Nivolumab in Lung Cancer Section 3.1 Study Design and Duration, Table 5.1-3 Off-treatment Follow-up Assessments	Modified follow-up for overall survival for 3 years	With a reduction in maximum duration of nivolumab treatment to 2 years-and subsequent decreased number of meaningful events, the follow-up was changed to a minimum of 3 years.
Study schematic, Study Design, Section 1.1 Study Rationale, Section 4.5 Selection and Timing of Dose for Each Subject	Added rationale for maximum treatment duration with nivolumab of 2 years	Collective data suggests minimal benefit derived from continuing I-O treatment beyond two years in advanced tumors.
Section 8.1 Sample Size Determination Section 8.3.1 Primary Endpoint(s) Section 8.4.2 Efficacy Analyses Section 8.5 Interim Analyses	Alpha adjustment between the two co-primary endpoints was removed.	With the early stop of enrollment and consequent reduced number of subjects, demonstration of non-inferiority statistically is no longer an objective due to insufficient power.
Study schematic, Synopsis, Section 8.1 Sample size Determination	Sample size reduced	With the approval of nivolumab 480 mg every 4 weeks in the US for NSCLC and increasing use of immunotherapy in earlier lines of therapy, BMS decided to stop enrollment.
Section 8.3.1 Primary Endpoint(s)	Primary endpoint was modified	To incorporate censoring for subsequent therapy which was missed in the original protocol.
Table 5.1-1 Screening Procedural Outline Table 5.1-2 On-Treatment Assessments Table 5.1-3 Off-treatment Follow-Up Assessments	Amylase and lipase were removed from required laboratory tests	Asymptomatic laboratory abnormalities for amylase and lipase do not require dose delay or discontinuation.

SYNOPSIS

Clinical Protocol CA209384

Protocol Title: A Dose Frequency Optimization, Phase IIIB/IV Trial of Nivolumab 240 mg Every 2 Weeks vs Nivolumab 480 mg Every 4 Weeks in Subjects with Advanced or Metastatic Non-small Cell Lung Cancer who Received Up to 12 Months of Nivolumab at 3 mg/kg or 240 mg Every 2 Weeks

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Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Nivolumab at 240 mg every 2 weeks as a 30-minute (± 5 minutes) intravenous (IV) infusion or nivolumab 480 mg every 4 weeks as a 30-minute (± 5 minutes) IV infusion until disease progression, unacceptable toxicity, or withdrawal of informed consent for up to 2 years.

Study Phase: 3b/4

Research Hypothesis: Progression-free survival (PFS) rate at 6 months and at 1 year after randomization in subjects receiving nivolumab 480 mg every 4 weeks (Arm 2) will be similar to the PFS rate in subjects receiving nivolumab 240 mg every 2 weeks (Arm 1) for the treatment of advanced/metastatic (Stage IIIb/IV) non-small cell lung cancer (NSCLC; non-Squamous [non-Sq] and Squamous [Sq]) after receiving up to 12 months of nivolumab 3 mg/kg or 240 mg every 2 weeks prior to enrollment.

Objectives: The coprimary objectives are to compare PFS rate at 6 months after randomization and PFS rate at 1 year after randomization, as measured by investigator-assessed response using Response Evaluation Criteria in Solid Tumor (RECIST) 1.1 criteria, of nivolumab 240 mg every 2 weeks (Arm 1) and nivolumab 480 mg every 4 weeks (Arm 2) in subjects with advanced/metastatic (Stage IIIb/IV) NSCLC (non-Sq and Sq).

The secondary objectives are:

- To compare PFS rate in Arms 1 and 2 at 1 year after randomization by tumor histology and by response before randomization
- To compare PFS rate at 2 years after randomization in Arms 1 and 2
- To compare the overall survival (OS) rate at 1 year after randomization and up to 3 years after randomization in Arms 1 and 2, in all treated subjects, by tumor histology, and by response criteria before randomization
- To assess safety and tolerability of nivolumab, as measured by the incidence and severity of adverse events (AEs) and specific laboratory abnormalities, in all treated subjects, in Arms 1 and 2, by tumor histology and response before randomization

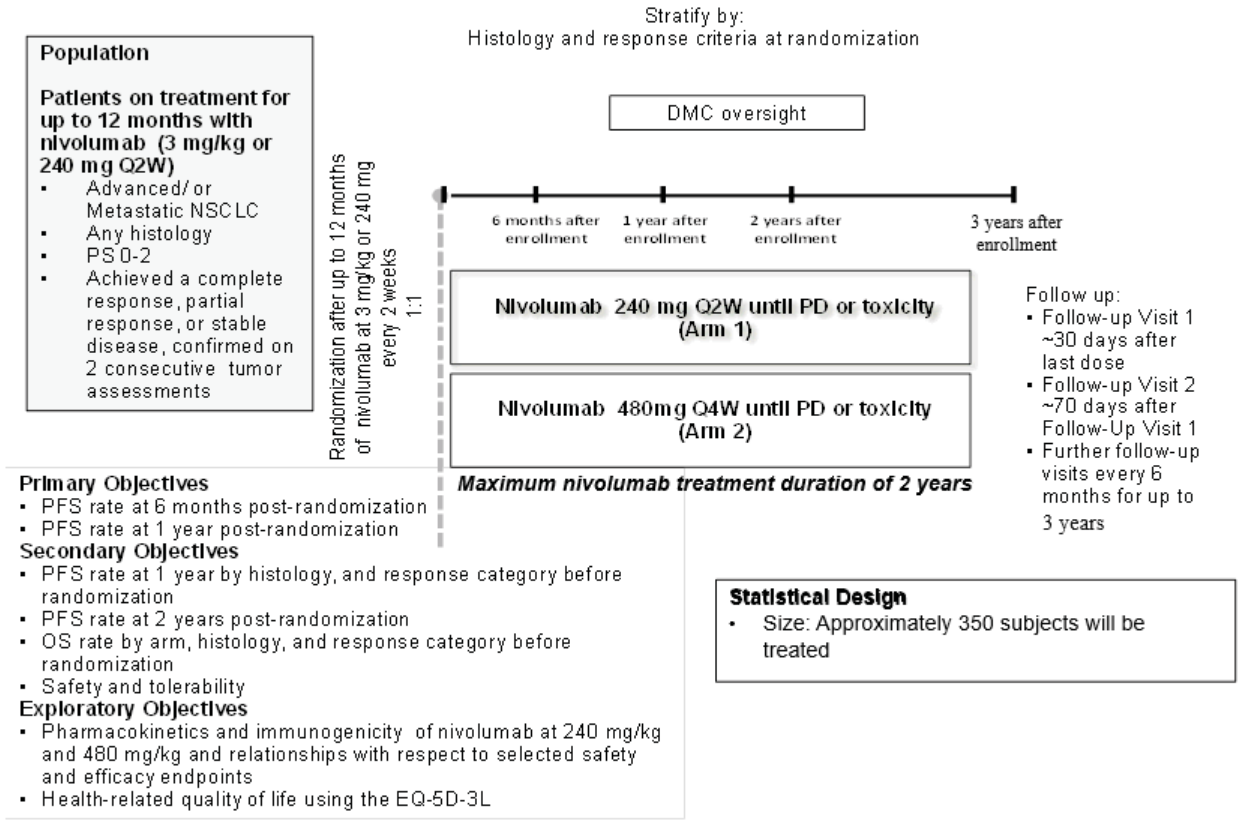
The exploratory objectives are:

- To characterize the pharmacokinetics of nivolumab at 240 mg and 480 mg and to explore relationships with respect to selected safety and efficacy endpoints
- To characterize the immunogenicity of nivolumab at 240 mg and 480 mg
- To assess health-related quality of life using the EQ-5D-3L

Study Design: Subjects will have received up to 12 months (52 weeks) of nivolumab therapy at either 3 mg/kg or 240 mg every 2 weeks and achieved a complete response (CR), partial response (PR), or stable disease (SD) as evidenced by 2 consecutive tumor assessments prior to enrollment. At enrollment, subjects will be randomized 1:1 to receive either 240 mg every 2 weeks (Arm 1) or 480 mg every 4 weeks (Arm 2). Randomization will be stratified by histology and response criteria to pre-study nivolumab at randomization (CR or PR vs SD). For subjects receiving nivolumab 240 mg every 2 weeks, each 14-day dosing period will constitute a cycle. For subjects receiving nivolumab 480 mg every 4 weeks, each 28-day dosing period will constitute a cycle. Investigational product will be provided at randomization.

Subjects will continue treatment until disease progression or unacceptable toxicity for a maximum of 2 years from their first randomized dose. The follow-up period begins when the decision to permanently discontinue a subject from study therapy is made (no further treatment or retreatment with nivolumab is anticipated).

Study Schematic



Study Population:

Key Inclusion Criteria:

a) Subjects with histologically or cytologically documented Sq- or non-SqNSCLC who present with Stage IIIB/Stage IV disease (according to version 7 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology), or with recurrent or progressive disease following multimodal therapy (radiation therapy, surgical resection, or definitive chemoradiotherapy for locally advanced disease).

b) Subjects must have received and tolerated nivolumab 3 mg/kg or 240 mg every 2 weeks for up to 12 months (52 weeks). Subjects may continue to receive pre-study nivolumab treatment during screening assessments.

c) Subjects must have at least 2 consecutive tumor assessments confirming CR, PR, or SD to the pre-study nivolumab treatment (latest scan must be performed within 28 days prior to randomization).

d) Subjects must have had measurable disease by CT or MRI per RECIST 1.1 criteria at the time of starting first dose of pre-study nivolumab treatment.

e) As of Amendment 01, this criterion is no longer applicable.

i) As of Amendment 01, this criterion is no longer applicable.

ii) As of Amendment 01, this criterion is no longer applicable.

iii) As of Amendment 01, this criterion is no longer applicable.

iv) As of Amendment 01, this criterion is no longer applicable.

v) Subjects with a known activating epidermal growth factor receptors (EGFR) mutation or anaplastic lymphoma kinase (ALK) translocation are eligible if they have received an EGFR or ALK TKI in addition to a platinum-based chemotherapy

vi) As of Amendment 01, this criterion is no longer applicable.

f) Eastern Cooperative Oncology Group (ECOG) PS 0-2

Key Exclusion Criteria

a) Subjects with carcinomatous meningitis

b) Subjects with untreated, symptomatic CNS metastases are excluded

c) Subjects with interstitial lung disease (eg, sarcoidosis) that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity. Subjects with chronic obstructive pulmonary disease whose disease is controlled at study entry are allowed.

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

Study Drug for CA209384		
Medication	**Potency**	**IP/Non-IP**
Nivolumab	100 mg (10 mg/mL)	IP

Study Assessments: Safety assessments will be conducted throughout the trial and during 100 days after the last dose of study treatment. The assessments are described in the Time and Events Schedule and should be monitored starting on Cycle 1 Day 1 until discontinuation from study therapy. National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0 will be the criteria used to assess severity of AEs. Efficacy assessments will take place according to the Time and Events Table. Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible. Changes in tumor measurements and tumor responses to guide ongoing study treatment decisions should be assessed by the investigator using RECIST 1.1.

Samples for pharmacokinetic (PK) and immunogenicity assessments will be collected for all subjects receiving nivolumab. All time points are relative to the start of study drug administration.

The EQ-5D-3L comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety) and a visual analog rating scale. The responses to the EQ-5D-3L domains will be converted to health status index based on the European scoring algorithm.

Statistical Considerations:

Sample Size: The primary analyses evaluates the non-inferiority of post-randomization 6-months and 12-month milestone PFS rate of nivolumab 480 mg Q4W versus the PFS rate of nivolumab 240 mg Q2W in subjects with disease control (CR/PR/SD) after receiving up to 12 months (52 weeks) of nivolumab 3 mg/kg or 240 mg Q2W treatment. The non-inferiority margin of -10% was chosen for this study. Patients who received nivolumab for up to 12 months (52 weeks) and achieved CR, PR, or SD confirmed by 2 consecutive tumor assessments will be randomized. It is estimated that the 12-month milestone PFS rate post-randomization is 0.48 with 240 mg Q2W and 6-month PFS rate post-randomization is 0.63.

The sample size was computed based on a cumulative hazard function which accounts for both progression and censoring distributions. Using cumulative hazard function and its relation with survival function, it is estimated that 620 patients, 310 in each arm, will provide 80% power for the lower bound of a 95.2% one-sided confidence interval

above -10% at the 12-month milestone and the lower bound of a 99.3% confidence interval above -10% at 6 months if PFS rates of the 2 arms are assumed to be equal. The experiment-wise error rate is maintained at one-sided 5% level.

To account for those who are randomized but not receiving treatment, 320 per arm will be randomized. With a 15% screen failure rate, approximately 753 subjects will be screened to achieve approximately 640 randomized subjects.

UPDATE as of revised protocol 05: Due to early stop of enrollment of the study, the sample size will be the number of subjects randomized after enrolment stops. Approximately 350 subjects are expected to be randomized and receive study treatment. Since the number of subjects was reduced significantly, there is not enough power to demonstrate non-inferiority of the two treatment regimens. Hence the adjustment of alpha between 6 months and 12 months PFS rates (as originally planned) will not be conducted. Instead, 95% one-sided confidence interval around the difference of PFS rates will be generated.

Endpoints: Primary Endpoints: The co-primary objectives of this trial will be assessed by PFS rate at 6 months after randomization and PFS rate at 1 year after randomization. PFS is defined as the time from the date of randomization to the date of first documented tumor progression determined by the investigator or death, whichever is earlier. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment.

Subjects who did not have any on-study tumor assessments and did not die will be censored on the first dosing date. Subjects who received any subsequent anti-cancer therapy (including on-treatment palliative radiation therapy of non-target bone lesions or CNS lesions) without a prior reported progression will be censored at the last evaluable tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy.

The PFS rate at 6 months is the rate from Kaplan-Meier (KM) estimate 6 months after randomization; PFS rate at 1 year is the rate from KM estimate at 1 year after randomization.

Secondary objectives will be assessed by:

- PFS rate at 1 year after randomization by tumor histology and by response criteria
- PFS rate at 2 years after randomization
- OS rate at 1 year and OS up to 3 years by arm, histology, and response status at randomization. OS is defined as time from the date of randomization to the date of death. Subjects who did not die by the end of the study will be censored at the last known date alive. OS rate at 1 year is the rate from KM estimated at 1 year after randomization.
- Safety and tolerability of nivolumab, as measured by incidence and severity of AEs and specific laboratory abnormalities

Exploratory endpoints will be assessed by:

- Relationship of pharmacokinetics and immunogenicity of nivolumab with respect to selected safety and efficacy endpoints at 240 mg Q2W and 480 mg Q4W
- EQ-5D-3L

Analyses: Efficacy analyses: PFS will be summarized by KM product-limit method and confidence interval for hazard ratio will be produced from a stratified (by tumor histology and response category) proportional hazard model. Median values of PFS, along with one-sided 95% CI using the Brookmeyer and Crowley method, will be calculated. The status of subjects who are censored in the PFS KM analysis will be tabulated for each dose regimen.

The 95% one-sided confidence intervals for PFS rates at 6 and 12 months will be calculated using the Greenwood formula for each dose regimen and difference between dose regimens.

The OS and OS rates at 6 months and 12 months will be analyzed using the same method as for PFS and PFS rates.

Safety analysis: Safety will be analyzed through the incidence of deaths, AEs, serious adverse events (SAEs), AEs leading to discontinuation, AEs leading to dose interruption, select AEs, and specific laboratory abnormalities (worst grade) in each arm. Toxicities will be graded using the NCI CTCAE version 4.0.

Pharmacokinetic Analysis: The nivolumab serum concentration data from this study may be combined with data from other nivolumab studies in the population pharmacokinetic model. These models may be used to evaluate the effects of intrinsic and extrinsic covariates on the pharmacokinetics of nivolumab and to determine measures of individual

exposure. In addition, model determined exposures may be used for exposure-response analyses. Results of population pharmacokinetics and exposure-response analyses will be reported separately.

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

Subject's overall health state on a visual analog scale (EQ-VAS) at each assessment time point as well as change from baseline will be summarized using descriptive statistics by arm (including mean and 95% confidence interval), as randomized.

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

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1 INTRODUCTION AND STUDY RATIONALE

The approved treatment options for locally advanced or metastatic non-small cell lung cancer (NSCLC) have been limited. Approximately 85% of lung cancer is NSCLC. Of these, approximately 80% are non-squamous (non-Sq) and 20% are squamous (Sq) histology.

Despite treatment with platinum- and taxane-based chemotherapy, patients with metastatic NSCLC have a median overall survival (OS) of 10 months and a 5-year survival rate of ~15%.[1] Data are emerging that suggest patients with SqNSCLC may have a worse prognosis and fewer therapeutic options than patients with other histologies. Pivotal studies of first-line and second-line therapy have indicated that, in contrast to non-SqNSCLC, patients with SqNSCLC do not derive benefit from newer agents such as pemetrexed or bevacizumab.[2,3] Similarly, activating mutations in epidermal growth factor receptors (EGFR) that render lung tumors sensitive to EGFR-targeted tyrosine kinase inhibitors (EGFR-TKIs) are found in only approximately 2.7% of SqNSCLC cases.[4]

Despite the increased number of treatment options available for patients with non-SqNSCLC, there have been little OS improvements from several new agents, including pemetrexed and bevacizumab. Therapeutic options for mutation wild-type non-SqNSCLC are particularly limited after failure of front-line chemotherapy. With the development of targeted agents for patients with tumors with driver mutations in the EGFR or anaplastic lymphoma kinase (ALK), some improvement in progression-free survival (PFS) is realized, but, as a consequence of acquired resistance, the improvement in OS is still limited. Overall, this group of patients only has an OS of about 8 months after progression from platinum agents. Once resistance to TKIs occurs, the patients who have EGFR mutations or ALK translocations will have rapid disease progression.

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 carcinoma (RCC), and nonsmall cell lung cancer (NSCLC).

Nivolumab is in clinical development for the treatment of patients with NSCLC, RCC, melanoma, squamous cell carcinoma of the head and neck (SCCHN) and other tumors (eg, glioblastoma multiforme, mesothelioma, small cell lung cancer, gastric). Opdivo® is approved in the United States, European Union, and other countries for the treatment of patients with unresectable or metastatic melanoma, advanced NSCLC with progression on or after platinum-based chemotherapy, advanced RCC whose disease progressed on an antiangiogenic therapy (US only) and classical Hodgkin lymphoma that has relapsed or progressed after autologous hematopoietic stem cell transplantation and post-transplantation brentuximab vedotin treatment (US only).

In general, nivolumab has also been well-tolerated to date with a favorable safety profile relative to anticipated toxicities based on its immunostimulatory mechanism of action.[5]

Decreasing the frequency of administration of nivolumab has the potential for improved convenience in patients with lung cancer. The development of nivolumab is ongoing to provide additional data on the optimal dose and frequency of nivolumab administration that balances quality of life and compliance for patients in addition to efficacy and safety. This study will evaluate the outcomes of a less frequent dose administration (480 mg every 4 weeks vs 240 mg every 2 weeks).

1.1 Study Rationale

A less frequent nivolumab dose administration (480 mg every 4 weeks instead of 240 mg every 2 weeks) could improve adherence while maintaining efficacy for those patients who may need to continue therapy for long periods of time. The results of this study will allow for greater understanding of the efficacy and safety profiles of a less frequent dose and will provide information on how physicians may incorporate this dosing regimen into their practice. While additional regimen questions, such as the appropriate duration of therapy and benefit of retreatment, exist, other Bristol-Myers Squibb (BMS)-sponsored studies and investigator-sponsored studies will address some of these questions.

This is an open-label, randomized, Phase 3b/4 study in adult subjects with advanced/metastatic (Stage IIIb/IV) NSCLC (non-Sq and Sq). Approximately 350 patients will be randomized 1:1 into 2 different dose regimens of nivolumab for a maximum of 2 years.

Rationale for Dose and Schedule of Nivolumab

All patients will receive nivolumab (3 mg/kg or 240 mg) every 2 weeks for up to 12 months (52 weeks) and achieve a complete response (CR), partial response (PR), or stable disease (SD) to the nivolumab treatment confirmed on 2 consecutive tumor assessment prior to enrollment. After this pre-study period, subjects will be enrolled, screened, and randomized into 1 of 2 arms.

The dose and schedule of nivolumab for Arm 1 will be 240 mg IV every 2 weeks (Q2W). This is based on the expected similarity of safety and efficacy to approved 3 mg/kg Q2W dosing regimen in advanced lung cancer. Nivolumab monotherapy has been extensively studied in the NSCLC patient population in CA209003, CA209063, CA209017, CA209057, and CA209012 with body-weight normalized dosing (mg/kg) and has shown improved survival at 3 mg/kg Q2W. The population pharmacokinetics (PPK) has demonstrated that body-weight normalized dosing produced relatively uniform exposures in subjects with a wide range of body weights at the current dose of 3 mg/kg. Using the PPK model, simulations predict that a flat dose of 240 mg of nivolumab Q2W would produce similar exposures to those following 3 mg/kg Q2W with greater exposures predicted in subjects with lower body weight (< 60 kg) and slightly lower exposures in higher body weights (> 100 kg). However, based on a wide therapeutic window of nivolumab monotherapy, the range of exposures with flat dosing are not expected to affect efficacy because the exposures predicted for the 240-mg dose are on the flat part of the exposure-response curve. For safety, doses up to 10 mg/kg nivolumab Q2W have been well tolerated across multiple tumors and an increase in exposure is not associated with a probability of increasing AEs leading to discontinuation. While subjects in the lower body weight range (< 50 kg), which account for < 5% of subjects in the clinical programs, would have greater exposures,

the exposures are predicted to be within the range of observed exposures at doses (up to 10 mg/kg) used in the nivolumab clinical program and are not considered to put subjects at increased risk. Therefore, a flat dose of 240 mg for nivolumab monotherapy is recommended for further investigation in this study.

Subjects randomized to Arm 2 will receive nivolumab 480 mg every 4 weeks. The every 4-week schedule (Q4W) will be more convenient for subjects. Based on pharmacokinetic modeling, the 480 mg Q4W (after steady state is reached with 3 mg/kg or 240 mg every 2 weeks) will provide steady-state average concentrations similar to 3 mg/kg or 240 mg Q2W, which has been shown to provide longer survival in NSCLC patients. However, 480 mg Q4W is expected to result in higher (approximately 20%) steady-state maximum concentration (peaks), and lower (approximately 10%) steady-state trough concentrations compared to steady state of 3 mg/kg Q2W. Nivolumab was adequately tolerated up to 10 mg/kg, the highest dose level tested, and no maximum tolerated dose was identified. In addition, the exposure-response relationship for safety is flat. Thus, a slight increase in the steady-state maximum concentration is not expected to increase the safety risk of nivolumab. However, a marginal decrease in steady-state trough concentration is not expected to reduce the efficacy as high trough concentrations and > 90% intra-tumoral receptor occupancy are still maintained at 480 mg Q4W dose. Nivolumab 480 mg Q4W is expected to have similar efficacy and safety profile to 3 mg/kg Q2W.

Tumor Assessments

Subjects are expected to have already completed their initial and second tumor assessments prior to enrollment. Once enrolled in this study, tumor assessments will continue every 8 weeks, which is similar to the standard of care assessment in this population.

1.2 Research Hypothesis

PFS rate at 6 months and at 1 year after randomization in subjects receiving nivolumab 480 mg every 4 weeks (Arm 2) will be similar to the PFS rate in subjects receiving nivolumab 240 mg every 2 weeks (Arm 1) for the treatment of advanced/metastatic (Stage IIIb/IV) NSCLC (non-Sq and Sq) after receiving up to 12 months of nivolumab (3 mg/kg or 240 mg every 2 weeks) prior to enrollment.

1.3 Objectives(s)

1.3.1 Primary Objectives

The coprimary objectives are to compare PFS rate at 6 months after randomization and PFS rate at 1 year after randomization, as measured by investigator-assessed response using Response Evaluation Criteria in Solid Tumor (RECIST) 1.1 criteria, of nivolumab 240 mg every 2 weeks (Arm 1) and nivolumab 480 mg every 4 weeks (Arm 2) in subjects with advanced/metastatic (Stage IIIb/IV) NSCLC (non-Sq and Sq).

1.3.2 Secondary Objectives

- To compare PFS rate in Arms 1 and 2 at 1 year after randomization by tumor histology and by response criteria before randomization
- To compare PFS rate at 2 years after randomization in Arms 1 and 2

- To compare the OS rate at 1 year after randomization and up to 3 years after randomization in Arms 1 and 2, in all treated subjects, by tumor histology, and by response criteria before randomization
- To assess safety and tolerability of nivolumab, as measured by the incidence and severity of AEs and specific laboratory abnormalities, in all treated subjects, in Arms 1 and 2, by tumor histology, and response criteria before randomization

1.3.3 Exploratory Objectives

- To characterize the pharmacokinetics of nivolumab at 240 mg and 480 mg and to explore relationships with respect to selected safety and efficacy endpoints
- To characterize the immunogenicity of nivolumab at 240 mg and 480 mg
- To assess health-related quality of life using the EQ-5D-3L

1.4 Product Development Background

1.4.1 Efficacy of Nivolumab in Lung Cancer

Nivolumab monotherapy is approved in the United States, European Union, and other countries for the treatment of patients with unresectable or metastatic melanoma, advanced NSCLC with progression on or after platinum-based chemotherapy, advanced RCC whose disease progressed on an antiangiogenic therapy (US only) and classical Hodgkin lymphoma that has relapsed or progressed after autologous hematopoietic stem cell transplantation and post-transplantation brentuximab vedotin treatment (US only).At the time of study initiation, the recommended dose of nivolumab in advanced NSCLC is 3 mg/kg administered as an IV infusion over 60 minutes (± 10 minutes) every 2 weeks until disease progression, or unacceptable toxicity. In April 2018, the USPI for NSCLC was updated to nivolumab 240 mg every 2 weeks or nivolumab 480 mg every 4 weeks administered as an IV infusion over 30 minutes.

Nivolumab Monotherapy Compared to Docetaxel in Patients with Squamous Cell Non-small Cell Lung Cancer - CA209017

Study CA209017 was an open-label, randomized Phase 3 trial of nivolumab vs docetaxel in previously treated advanced or metastatic SqNSCLC. In this study, subjects were randomized 1:1.[6] A total of 272 patients with metastatic SqNSCLC who had experienced disease progression during or after 1 prior platinum, doublet-based chemotherapy regimen were enrolled. Patients received nivolumab (n=135) administered intravenously at 3 mg/kg every 2 weeks or docetaxel (n=137) administered intravenously at 75 mg/m^2 every 3 weeks. This study included patients regardless of their PD-L1 status. The trial excluded patients with autoimmune disease, symptomatic interstitial lung disease, or untreated brain metastasis. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrollment, and either off corticosteroids, or on a stable or decreasing dose of < 10 mg daily prednisone equivalents. The first tumor assessments were conducted 9 weeks after randomization and continued every 6 weeks thereafter.

The primary endpoint was OS. In this trial, the median age was 63 years (range: 39 to 85) with 44% ≥ 65 years of age and 11% ≥ 75 years of age. The majority of patients were white (93%)

and male (76%). Baseline Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) was 0 (24%) or 1 (76%). Results demonstrated a statistically significant improvement in OS for patients randomized to nivolumab as compared with docetaxel at the prespecified interim analysis when 199 events were observed (86% of the planned number of events for final analysis) (Table 1.4.1-1).[6]

Table 1.4.1-1: CA209017 (Intent-to-Treat) Analysis

Prespecified Interim Analysis	Nivolumab (n = 135)	Docetaxel (N = 137)
Events (%)	86 (64%)	113 (82%)
1-yr PFS % (95% CI)	21 (14, 28)	6 (3, 12)
Median survival in months (95% CI)	9.2 (7.3, 13.3)	6.0 (5.1, 7.3)
P value[a]	0.00025	
Hazard ratio (95% CI)[b]	0.59 (0.44, 0.79)	

[a] P value is derived from log-rank test stratified by region and prior paclitaxel use; the corresponding O'Brien-Flemming efficacy boundaries significance level is 0.0315.

[b] Derived from stratified proportional hazards model.

In a 24 month analysis, nivolumab continued to provide an improved OS and PFS compared to docetaxel. OS was 23% in the nivolumab group and 8% in the docetaxel group. PFS was 16% in the nivolumab group and not reported in the docetaxel group. Benefit to nivolumab was observed independently of PD-L1 status.

Nivolumab Monotherapy Compared to Docetaxel in Patients with Non-Squamous Cell Non-Small Cell Lung Cancer - CA209057

Study CA209057 was a randomized, Phase 3 trial. Patients with stage IIIB/IV or recurrent non-SqNSCLC who received at least 1 prior platinum-doublet chemotherapy were randomized 1:1 to receive either 3 mg/kg of nivolumab every 2 weeks or docetaxel 75 mg/m^2 every 3 weeks. The nivolumab group enrolled 292 patients, and the docetaxel group enrolled 290 patients.[7] A 27% decrease in risk of death was observed in the nivolumab group compared to the docetaxel group (hazard ratio, 0.73; 96% CI, 0.59, 0.89, P = 0.002). OS was significantly improved in the nivolumab group (12.2 months, 95% CI, 9.7, 15.0) compared to the docetaxel group (9.4 months, 95% CI, 8.1, 10.7). In addition, the OS rate for those subjects with PD-L1 expression was nearly double in the nivolumab group compared to the docetaxel group (by ≥ 10%, 19.4 months vs 8 months; ≥ 5%, 18.2 vs 8.1 months; ≥ 1%, 17.2 vs 9.0 months).[7] The 1-year survival rate for the nivolumab group was 51% compared to 39% in the docetaxel group. The 1-year PFS in the nivolumab group was 19% and 8.1% in the docetaxel group.[7] In a 24 month analysis, nivolumab continued to provide an improved efficacy profile of docetaxel. The OS in the nivolumab group was 29% and 16% in the docetaxel group. The 2-year PFS in the nivolumab group was 12% and 1% in the docetaxel group.

Summary

There are currently 5 trials in the clinical development program looking at the activity of nivolumab in first-, second-, and third-line treatment of NSCLC[8]:

- CA209012: A multi-arm Phase 1 safety study of nivolumab in combination with gemcitabine/cisplatin, pemetrexed/cisplatin, carboplatin/paclitaxel, bevacizumab maintenance, erlotinib, ipilimumab, or as monotherapy in subjects with stage IIIB/IV NSCLC.
- CA209026: An open-label, randomized Phase 3 trial of nivolumab vs investigator's choice chemotherapy as first-line therapy for stage IIIB/IV or recurrent NSCLC.
- CA209153: An open-label, randomized, Phase 3b/4 safety trial of nivolumab in subjects with advanced or metastatic NSCLC who have progressed during or after receiving at least 1 prior systemic regimen.
- CA209171: An open-label trial with nivolumab in subjects with advanced or metastatic SqNSCLC who received at least 1 prior systemic regimen.
- CA209227: An open-label, randomized trial of nivolumab, nivolumab plus chemotherapy, or nivolumab plus ipilimumab vs platinum doublet chemotherapy in subjects with chemotherapy-naive Stage IV or recurrent NSCLC.

The Investigator Brochure (IB) will be updated with the final results of these studies as data become available.

1.4.2 Adverse Effects with Nivolumab Monotherapy

CA209017

In the Phase 3 study CA209017, the primary population for safety analyses was all treated subjects (260 total: 131 subjects in the nivolumab group and 129 subjects in the docetaxel group). The comparative safety data demonstrated that nivolumab monotherapy has a favorable safety profile as compared to docetaxel, including both hematologic and non-hematologic toxicities, in subjects with previously-treated advanced SqNSCLC. The overall safety profiles of both nivolumab and docetaxel (Table 1.4.2-1) were consistent with expectations based on prior data in terms of the type, frequency, and severity of reported events, and no new safety concerns with nivolumab monotherapy treatment were identified.[9]

- No subjects in the nivolumab group died due to study drug toxicity. In the docetaxel group, 3 deaths (2.3%) were attributed to study drug toxicity.
- The frequency of all causality AEs and serious adverse events (SAEs) of any grade were similar across treatment groups. Numerically lower rates of Grade 3-4, all-causality AEs, and SAEs, as well as rates of both all-causality and drug-related AEs leading to discontinuation, were observed in the nivolumab group as compared to the docetaxel group.
- Drug-related AEs (any grade and Grade 3-4) were reported less frequently in the nivolumab group than in the docetaxel group. In the nivolumab group, no individual Grades 3-4 drug-related AEs occurred in more than 1 subject (0.8%), and no subject experienced a Grade 5 drug-related AE. The higher rates of both all-grade and Grades 3-4 drug-related AEs in the

docetaxel group were mainly attributable to hematological toxicities and infections, consistent with the myelosuppressive profile of docetaxel.

- Fatigue (16.0%) was the only drug-related, any-grade AE that occurred in ≥ 15% of subjects in the nivolumab group. The most frequently reported drug-related any-grade AEs (≥ 15% of subjects) in the docetaxel group were neutropenia, fatigue, alopecia, nausea, anemia, and diarrhea.
- In the nivolumab group, all-causality select AEs (all-grade) were most frequently reported (≥ 10% of subjects) in the skin and GI categories.
- Grades 3-4 select AEs were reported by ≤ 3% of subjects in the nivolumab group in all select AE categories. Across categories, there were only 2 Grades 3-4 drug-related select AEs reported in the nivolumab group: 1 Grade 3 event of tubulointerstitial nephritis and 1 event of Grade 3 colitis. One additional Grade 3 event of pneumonitis was changed from not drug-related to drug-related after database lock.[9]
- Most patients who experienced treatment-related, select AE experienced the AE within 3 months of the first dose of nivolumab.[8]
- For nivolumab-treated subjects, the safety profile within pre-defined subgroups (age, gender, race, and region) was consistent with the overall safety profile.
- Abnormalities in hematology laboratory results, liver function tests, and kidney function tests in nivolumab treated subjects were primarily Grades 1-2 in severity. The only Grades 3-4 abnormality reported in > 5% of subjects in the nivolumab group was absolute lymphocyte decrease (no Grades 3-4 abnormalities in hepatic or kidney function tests occurred in the nivolumab group). The majority of subjects in the nivolumab group had normal thyroid function at baseline and throughout the treatment period. A greater proportion of subjects experienced a high thyroid stimulating hormone (TSH) with low free T3/T4 while on treatment in the nivolumab group (9.5%) as compared to the docetaxel group (1.1%).
- Immunogenicity of nivolumab does not appear to be clinically meaningful based on low titers, no hypersensitivity/infusion site reactions in ADA positive subjects, and no evidence of loss of efficacy in neutralizing ADA positive subjects. Of the 109 nivolumab-treated subjects who had evaluable ADA data at baseline and on treatment in CA209017, 8 (7.3%) subjects were baseline positive, 21 (19.3%) subjects were positive for ADA, and 88 (80.7%) subjects were ADA negative. Of the 21 ADA-positive subjects, 1 (0.9%) subject was persistent positive based on 16 weeks definition and 3 (2.8%) subjects were positive for neutralizing ADAs at least at one time point[9]

Table 1.4.2-1: Summary of Select Adverse Events - All Treated Subjects[9]

	Number (%) of Subjects			
	All Causality		Drug Related	
	Nivolumab N=131	Docetaxel N = 129	Nivolumab N=131	Docetaxel N = 129
Select AE Category	71 (54.2)	68 (52.7)	41 (31.5)	46 (35.7)
Endocrine	9 (6.9)	3 (2.3)	5 (3.8)	0

Table 1.4.2-1: Summary of Select Adverse Events - All Treated Subjects[9]

	Number (%) of Subjects			
	All Causality		Drug Related	
	Nivolumab N=131	Docetaxel N = 129	Nivolumab N=131	Docetaxel N = 129
Grade 3-4[a]	0	0	0	0
Gastrointestinal	21 (16.0)	33 (25.6)	11 (8.4)	26 (20.2)
Grade 3-4[a]	3 (2.3)	4 (3.1)	1 (0.8)	3 (2.3)
Hepatic	3 (2.3)	5 (3.9)	2 (1.5)	2 (1.6)
Grade 3-4[a]	0	1 (0.8)	0	1 (0.8)
Pulmonary	7 (5.3)	3 (2.3)	6 (4.6)[b]	1 (0.8)
Grade 3-4	1 (0.8)	1 (0.8)	0[b]	0
Grade 5	0	1 (0.8)	0	1 (0.8)
Renal	7 (5.3)	3 (2.3)	4 (3.1)	3 (2.3)
Grade 3-4[a]	3 (2.3)	0	1 (0.8)	0
Skin	23 (7.6)	18 (14.0)	12 (9.2)	11 (8.5)
Grade 3-4[a]	1 (0.8)	2 (1.6)	0	2 (1.6)
Hypersensitivity/ Infusion Reactions	1 (0.8)	3 (2.3)	1 (0.8)	3 (2.3)
Grade 3-4[a]	0	1 (0.8)	0	1 (0.8)

[a] No Grade 5 events reported in the nivolumab group

[b] One Grade 3 event of pneumonitis (Subject [redacted]) changed from not drug-related to drug-related after database lock.

CA209057

Safety data from Study CA209057 demonstrate that nivolumab monotherapy has a favorable safety profile as compared to docetaxel, including both hematologic and non-hematologic toxicities, in subjects with metastatic or recurrent non-SqNSCLC. The overall safety profiles of both nivolumab and docetaxel (Table 1.4.2-2) were consistent with expectations based on prior data in terms of the type, frequency, and severity of reported events, and no new safety concerns with nivolumab monotherapy treatment were identified.[10]

Key safety findings are as follows:

- One death in the nivolumab group (encephalitis) and 1 death in the docetaxel group (febrile neutropenia) were assessed as study-drug associated. The death in the nivolumab group, although reported prior to database lock, had its causality changed after database lock.
- The overall frequency of all-causality SAEs (any grade and Grades 3-4) was similar between the treatment groups.
- Overall, the frequencies of all-causality AEs of any grade were similar between the treatment groups while the rates of Grades 3-4 AEs were lower in the nivolumab-treated group.
- Lower rates of drug-related AEs leading to discontinuation were observed in the nivolumab group compared to the docetaxel group.
- Drug-related SAEs and AEs (any grade and Grades 3-4) were reported less frequently in the nivolumab group than in the docetaxel group. The higher rates of both any grade and Grades 3-4 drug-related AEs in the docetaxel group were mainly attributable to hematological toxicities and general disorders.
- Fatigue (16.0%) was the only drug-related any-grade AE that occurred in ≥ 15% of subjects in the nivolumab group. The most frequently reported drug-related any-grade AEs (≥ 15% of subjects) in the docetaxel group were neutropenia, fatigue, nausea, alopecia, diarrhea, anemia, asthenia, and decreased appetite.
- For nivolumab-treated subjects, the safety profile within pre-defined subgroups (age, gender, race, and region) was consistent with the overall safety profile.
- Overall, the safety profiles of PD-L1 positive and PD-L1 negative subgroups (defined by the 5% expression level at pre-study [baseline]) were comparable.
- Select AEs were AEs of special clinical interest meeting defined criteria
- Most select AEs were low grade, resolved, and were manageable using the recommended treatment guidelines for early work-up and intervention.
  - In the nivolumab group, all-causality select AEs (any grade) were most frequently reported (≥ 15% of subjects) in the skin and gastrointestinal (GI) categories.
  - Grades 3-4 select AEs were reported in the endocrine, GI, hepatic, pulmonary, and skin categories in the nivolumab group, and were reported by ≤ 3% of subjects in these select AE categories.
- Abnormalities in hematology laboratory results, liver tests, and kidney function tests in nivolumab subjects were primarily Grade 1 or 2. The only Grades 3-4 abnormality reported in ≥ 5% of subjects in the nivolumab group was absolute lymphocyte decrease (12.2% Grade 3, 1.0% Grade 4). Grades 3-4 abnormalities in hepatic parameters that were reported in ≥ 2% of subjects were limited to aspartate aminotransferase (AST) (2.8%) and alanine aminotransferase (ALT) (2.4%). There were no Grades 3-4 abnormalities in creatinine in the nivolumab group. The majority of subjects in the nivolumab group had normal thyroid function at baseline and throughout the treatment period. A greater proportion of subjects experienced a high TSH with low free T3/T4 while on treatment in the nivolumab group (12.0%) as compared to the docetaxel group (2.4%).
- Of the 251 nivolumab subjects who had evaluable ADA data at baseline and on treatment in CA209057, most were negative for ADA (83%); 17% were positive for ADA, and 7% were

baseline positive. Of the 43 ADA-positive subjects, none were persistent positive, 3 subjects had one neutralizing ADA sample, 12 had ADA-positive status at the last sample collection only, and 31 had an ADA status of other positive. Overall, there was minimal impact on safety.[10]

Table 1.4.2-2: Summary of Safety Results - All Treated Subjects[10]

	Number (%) Subjects					
	Nivolumab N = 287			Docetaxel N = 268		
Deaths	185 (64.5)			204 (76.1)		
Within 30 Days of Last Dose	36 (12.5)			21 (7.8)		
Within 100 Days of Last Dose	93 (32.4)			76 (28.4)		
Due to Study Drug Toxicity	0[a]			1 (0.4)		
	Any Grade	**Grade 3-4**	**Grade 5[a]**	**Any Grade**	**Grade 3-4**	**Grade 5**
All SAEs	134 (46.7)	95 (33.1)	23 (8.0)	111 (41.4)	91 (34.0)	14 (5.2)
Drug-related SAEs	21 (7.3)	15 (5.2)	0	53 (19.8)	48 (17.9)	0
All AEs Leading to DC	48 (16.7)	38 (13.2)	3 (1.0)	58 (21.6)	34 (12.7)	2 (0.7)
Drug-related AEs Leading to DC	14 (4.9)	11 (3.8)	0	40 (14.9)	18 (6.7)	0
All AEs (Regardless of Causality)	280 (97.6)	132 (46.0)	23 (8.0)	265 (98.9)	180 (67.2)	14 (5.2)
Most Frequent AEs (≥20% of Any Grade)						
Fatigue	91 (31.7)	9 (3.1)	0	102 (38.1)	18 (6.7)	0
Decreased appetite	83 (28.9)	5 (1.7)	0	58 (21.6)	4 (1.5)	0
Cough	76 (26.5)	1 (0.3)	0	62 (23.1)	0	0
Constipation	66 (23.0)	2 (0.7)	0	45 (16.8)	2 (0.7)	0
Dyspnea	65 (22.6)	14 (4.9)	1 (0.3)	63 (23.5)	10 (3.7)	0
Nausea	63 (22.0)	5 (1.7)	0	80 (29.9)	2 (0.7)	0
Asthenia	59 (20.6)	10 (3.5)	0	62 (23.1)	11 (4.1)	0
Diarrhea	45 (15.7)	3 (1.0)	0	73 (27.2)	3 (1.1)	0
Anemia	34 (11.8)	5 (1.7)	0	68 (25.4)	12 (4.5)	1 (0.4)
Alopecia	4 (1.4)	0	0	70 (26.1)	0	0

Table 1.4.2-2: Summary of Safety Results - All Treated Subjects[10]

	Number (%) Subjects					
	Nivolumab N = 287			Docetaxel N = 268		
Neutropenia	2 (0.7)	1 (0.3)	0	87 (32.5)	75 (28.0)	0
	Any Grade	Grade 3-4	Grade 5 [a]	Any Grade	Grade 3-4	Grade 5
Drug-related AEs	199 (69.3)	30 (10.5)	0	236 (88.1)	144 (53.7)	0
Most Frequent AEs (≥15% of Any Grade)						
Fatigue	46 (16.0)	3 (1.0)	0	78 (29.1)	13 (4.9)	0
Nausea	34 (11.8)	2 (0.7)	0	70 (26.1)	2 (0.7)	0
Decreased appetite	30 (10.5)	0	0	42 (15.7)	3 (1.1)	0
Asthenia	29 (10.1)	1 (0.3)	0	47 (17.5)	6 (2.2)	0
Diarrhea	22 (7.7)	2 (0.7)	0	62 (23.1)	3 (1.1)	0
Anemia	6 (2.1)	1 (0.3)	0	53 (19.8)	7 (2.6)	0
Neutropenia	1 (0.3)	0	0	83 (31.0)	73 (27.2)	0
Alopecia	1 (0.3)	0	0	67 (25.0)	0	0

[a] One death was attributed to nivolumab (encephalitis); association to nivolumab was changed after database lock.

All events are within 30 days of the last dose of study drug, unless otherwise indicated.

1.5 Overall Risk/Benefit Assessment

Treatment options with chemotherapy and targeted therapy offer limited benefits in overall survival. Patients with squamous histology have a worse prognosis and do not benefit from new treatments. Newer agents have also provided limited improvement in OS for non-squamous patients. These patients face an unmet medical need. Nivolumab demonstrated survival benefit over standard of care docetaxel across histology in 2 randomized Phase 3 trials. In addition, the safety profile for the nivolumab-treated patients was favorable compared to docetaxel. 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 is characterized by immune-related toxicities, such as diarrhea, rash, pneumonitis, liver toxicity, and endocrinopathies, which are manageable with established algorithms.

The optimal dosing frequency of administration that balances a favorable safety and efficacy profile with convenience and adherence for the patient is not yet known. This trial requires patients to receive nivolumab therapy at 3 mg/kg or 240 mg Q2W for up to 12 months (52 weeks) and demonstrated clinical benefit (CR, PR, or SD) on 2 consecutive tumor assessments prior to the study enrollment.

In Study 209003, 296 patients were randomized to receive nivolumab at 1 mg/kg, 3 mg/kg, or 10 mg/kg. A maximum tolerated dose was not defined at the doses tested. Drug-related Grades 3 or 4 toxic effects occurred in 14% of patients who received nivolumab, suggesting no new safety signals. Established algorithms provide for successful management of immune-related AEs via drug delay or glucocorticoids. It was noted in CA209003 that approximately 80% of patients achieved a durable clinical benefit by 4 months after treatment. With a minimum follow-up of over 1 year, 45% of patients maintained their clinical response.

The results of this study will allow for greater understanding of the efficacy and safety of a less frequent dose and provide information on how physicians may incorporate this dosing regimen into their practice. To assure an ongoing favorable risk/benefit assessment for subjects enrolled into CA209384, an independent Data Monitoring Committee (DMC) will be used to monitor the safety and activity of the treatments throughout the conduct of the trial.

A pattern of immune-related adverse events has been defined, for which management algorithms have been developed; these are provided in Appendix 2. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms.

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 (eg, loss of medical licensure, debarment).

2.2 Institutional Review Board/Independent Ethics Committee

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

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

2.3 Informed Consent

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

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

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

Investigators must:

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

- Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
- Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
- Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.

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

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

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

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

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

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

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

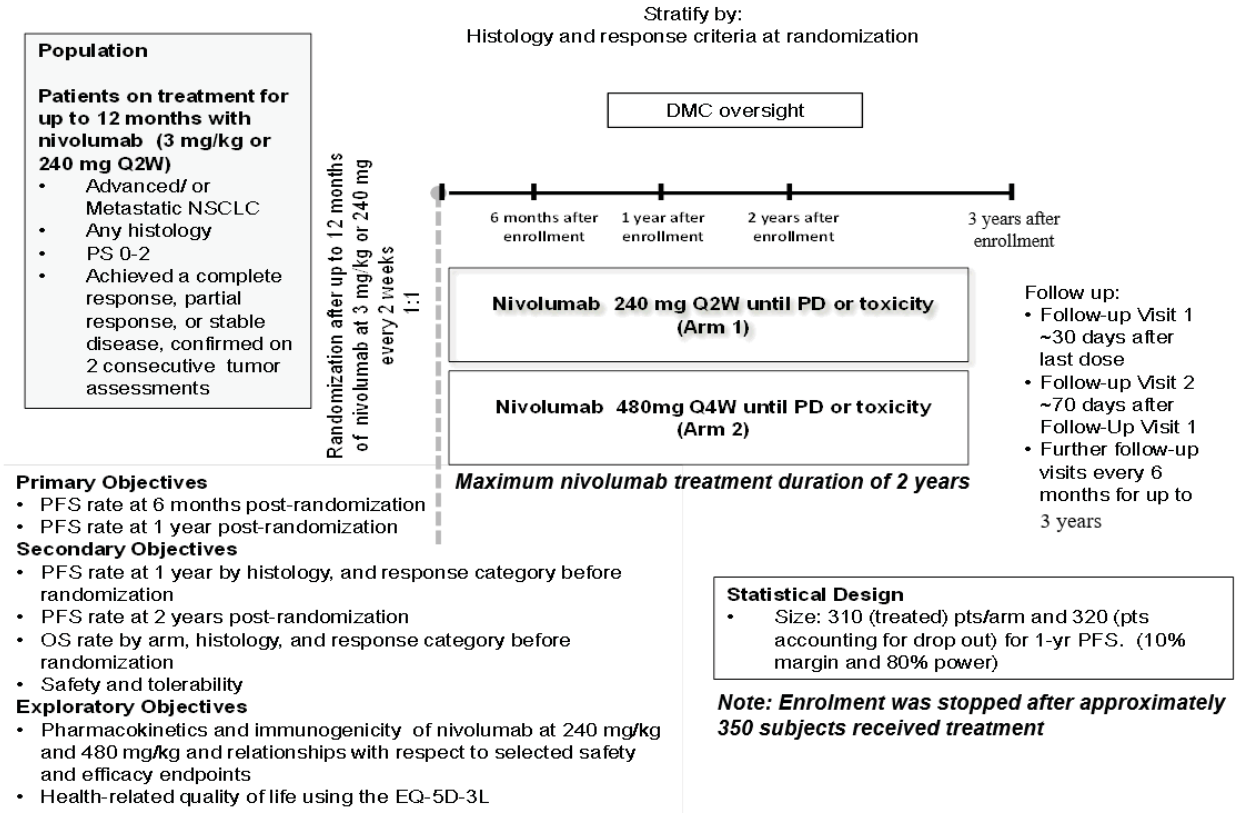
Subjects will have received up to 12 months (52 weeks) of nivolumab therapy at either 3 mg/kg or 240 mg every 2 weeks and achieved a CR, PR, or SD as evidenced by 2 consecutive tumor assessments prior to enrollment. At enrollment, subjects will be randomized 1:1 to receive either 240 mg every 2 weeks (Arm 1) or 480 mg every 4 weeks (Arm 2). Randomization will be stratified by histology and response criteria to pre-study nivolumab at randomization (CR or PR vs SD). For subjects receiving nivolumab 240 mg every 2 weeks, each 14-day dosing period will

constitute a cycle. For subjects receiving nivolumab 480 mg every 4 weeks, each 28-day dosing period will constitute a cycle. Investigational product will be provided at randomization.

Subjects will continue treatment until disease progression or unacceptable toxicity for a maximum of 2 years from their first randomized dose. The follow-up period begins when the decision to permanently discontinue a subject from study therapy is made (no further treatment or retreatment with nivolumab is anticipated) and will continue as specified in Table 5.1-3.

The study design schematic is presented in Figure 3.1-1.

Figure 3.1-1: Study Design Schematic



Each subject's last study visit will be defined as the last on-treatment or follow-up visit that occurs prior to the date of 3 years after the initiation of randomized therapy. The study will be completed no later than 3 years after the last subject's first visit.

3.2 Post Study Access to Therapy

At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive BMS-supplied study drug for the maximum treatment duration specified in protocol (Section 3.1). Study drug will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of BMS. BMS reserves the right to terminate access to BMS-supplied study drug if any of the following occur: a) the marketing application is rejected by

responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a government-sponsored or private health program; or d) therapeutic alternatives become available in the local market.

3.3 Study Population

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

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

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

b) Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests, and other requirements of the study.

2. Target Population

a) Subjects with histologically or cytologically documented Sq- or non-SqNSCLC who present with Stage IIIB/Stage IV disease (according to version 7 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology), or with recurrent or progressive disease following multimodal therapy (radiation therapy, surgical resection, or definitive chemoradiotherapy for locally advanced disease).

b) Subjects must have received and tolerated nivolumab 3 mg/kg or 240 mg every 2 weeks for up to 12 months (52 weeks). Subjects may continue to receive pre-study nivolumab treatment during screening assessments as noted in Table 5.1-2.

c) Subjects must have at least 2 consecutive tumor assessments confirming CR, PR, or SD to the pre-study nivolumab treatment (latest scan must be performed within 28 days prior to randomization).

d) Subjects must have had measurable disease by CT or MRI per RECIST 1.1 criteria at the time of starting first dose of pre-study nivolumab treatment.

e) As of Amendment 01, this criterion is no longer applicable.

i) As of Amendment 01, this criterion is no longer applicable.

ii) As of Amendment 01, this criterion is no longer applicable.

iii) As of Amendment 01, this criterion is no longer applicable.

iv) As of Amendment 01, this criterion is no longer applicable.

v) Subjects with a known activating EGFR mutation or ALK translocation are eligible if they have received an EGFR or ALK TKI in addition to a platinum-based chemotherapy

vi) As of Amendment 01, this criterion is no longer applicable.

f) ECOG PS 0-2

g) Subjects with stable CNS metastases are eligible if CNS metastases are treated and subjects have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to enrollment. In addition,

subjects must be either off corticosteroids or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent).

h) All baseline laboratory requirements will be assessed and should be obtained within 14 days (unless otherwise specified in Table 5.1-1) of first dose of randomized nivolumab. Screening laboratory values must meet the following criteria:

   i) WBCs ≥ 2000/μL

   ii) Neutrophils ≥ 1500/μL

   iii) Platelets ≥ 100 x 10^3/μL

   iv) Hemoglobin ≥ 9.0 g/dL

   v) Serum creatinine of ≤ 1.5 X ULN unless creatinine clearance > 40 mL/minute (measured or calculated using 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 ≤ 3X ULN

   vii) ALT ≤ 3X ULN

   viii) Total bilirubin ≤ 1.5X ULN (except subjects with Gilbert Syndrome who must have total bilirubin < 3.0 mg/dL)

i) Palliative radiotherapy must be completed at least 2 weeks prior to enrollment.

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

3. Age and Reproductive Status

a) Males and Females, ≥ 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 plus 5 half-lives of nivolumab plus 30 days (duration of ovulatory cycle) for a total of 5 months post-treatment completion.

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with nivolumab plus 5 half-lives of nivolumab plus 90 days (duration of sperm turnover) for a total of 7 months post-treatment completion. In addition, male subjects must be willing to refrain from sperm donation during this time.

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

See Appendix 3 for Women of Childbearing Potential Definitions and Methods of Contraception.

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Subjects with carcinomatous meningitis.

b) Subjects with untreated, symptomatic central nervous system (CNS) metastases are excluded.

2. Medical History and Concurrent Diseases

a) Subjects with interstitial lung disease (eg, sarcoidosis) that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity. Subjects with chronic obstructive pulmonary disease whose disease is controlled at study entry are allowed.

b) 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.

c) Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of first randomized dose of study drug with the exception of the subjects allowed to enroll with treated or active CNS metastases requiring steroids. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

d) Subjects who received prior therapy with an anti-CTLA-4, anti-PD-L1, or anti-PD-L2, anti-CT137 (or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways, except pre-study nivolumab) or subject is expected to require any other form of systemic antineoplastic therapy while receiving nivolumab.

e) Any other serious or uncontrolled medical disorder, active infection, physical exam finding, laboratory finding, altered mental status, or psychiatric condition that, in the opinion of the investigator, would limit the subject's ability to comply with the study requirements, substantially increase the risk to the subject, or impact the interpretability of study results.

f) Other active malignancy requiring concurrent intervention.

g) Subjects with previous malignancies (except non-melanoma skin cancers, and the following in situ cancers: bladder, gastric, colon, endometrial, cervical/dysplasia, melanoma, or breast) are excluded unless a complete remission was achieved at least 2 years prior to study entry AND no additional therapy is required during the study period with the exception of anti-estrogen/androgen therapy or bisphosphonates.

h) All toxicities attributed to prior anti-cancer therapy other than alopecia, fatigue, or peripheral neuropathy must have resolved to Grade 1 (NCI CTCAE version 4) or baseline before administration of study drug.

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

j) As of Amendment 01, this criterion has been moved to 3b.

k) Treatment with botanical preparations (eg herbal supplements or traditional Chinese medicines) intended for general health support or to treat the disease under study within 2 weeks prior to randomization/treatment.

3. Physical and Laboratory Test Findings

a) Any positive test result for hepatitis B virus or hepatitis C virus indicating presence of virus, e.g. Hepatitis B surface antigen (HBsAg, Australia antigen) positive, or Hepatitis C antibody (anti-HCV) positive (except if HCV-RNA negative).

b) Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at sites where mandated by local regulation

4. Allergies and Adverse Drug Reaction

a) History of severe hypersensitivity reactions to other monoclonal antibodies.

b) History of allergy or hypersensitivity to study drug components

5. Other Exclusion Criteria

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

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

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

3.3.3 Women of Childbearing Potential

Woman of childbearing potential 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.

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

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/mL at any time during the washout period, the woman can be considered postmenopausal.

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

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

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 3.4.3)
- Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of NSCLC)
- Any botanical preparation (eg herbal supplements or traditional Chinese medicines) intended to treat the disease under study or provide supportive care. Use of marijuana and its derivatives for treatment of symptoms related to cancer or cancer treatment are permitted if obtained by medical prescription or if its use (even without a medical prescription) has been legalized locally.

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.

3.4.3 Permitted Therapy

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

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

3.5 Discontinuation of Subjects following any Treatment with Study Drug

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

- Subject's request to stop study treatment
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Criteria described in Section 4.5.3

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. In the event a normal healthy female subject becomes pregnant during a clinical trial, the study drug must be discontinued immediately. In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). Please call the Medical Monitor within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

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

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

3.6 Post Study Drug Study Follow up

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

BMS may request that survival data be collected on all treated/randomized subjects outside of the protocol-defined window in Table 5.1-3. At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contacts or is lost to follow-up.

3.6.1 Withdrawal of Consent

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

3.6.2 Lost to Follow-Up

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

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

4 STUDY DRUG

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

- Study required premedication (if applicable)

Table 4-1: Study Drugs for CA209384

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
Nivolumab Solution for Injection	100 mg (10 mg/mL)	10 mL per vial/	5 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

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.

The investigational product in this study is nivolumab, which will be provided at randomization.

4.2 Non-investigational Product

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

Not applicable.

4.3 Storage and Dispensing

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

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

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

4.4 Method of Assigning Subject Identification

CA209384 is a randomized study. After the subject's eligibility is established and informed consent has been obtained, the subject will be enrolled, and a number will be assigned through an interactive web-based response system (IWRS). Specific instructions for enrollment and randomization procedures using IWRS will be provided to the investigational site in a separate document/manual. Subjects meeting all eligibility criteria and randomized into the study will be assigned to 1 of the 2 treatment arms and stratified by the following factors: histology and response at randomization (CR or PR vs SD).

Required information for registration includes, but is not limited to, the following:

- Response at randomization (CR or PR vs SD)

- Subject received and tolerated nivolumab either 3 mg/kg or 240 mg every 2 weeks for up to 12 months (52 weeks)
- ECOG status 0-2
- Planned date of randomization

Additional information required for registration in the study will be available in a separate document.

IWRS code will be provided to the analytical laboratories and to the PK and immunogenicity scientists to facilitate PK and immunogenicity sample analysis.

4.5 Selection and Timing of Dose for Each Subject

Subjects will be enrolled after receiving up to 12 months (52 weeks) of nivolumab therapy at 240 mg or 3 mg/kg Q2W and after achieving a CR, PR, or SD, confirmed on 2 consecutive tumor assessments.

Subjects in Arm 1 will receive 240 mg of nivolumab intravenously as a 30-minute (± 5 minutes) IV infusion on Day 1 of each treatment cycle every 2 weeks, until progression, unacceptable toxicity, withdrawal of consent, or the subject reaches a maximum of 2 years from the first on-study dose, or the study ends, whichever occurs first. In this arm, each 14-day dosing period will constitute a cycle.

Subjects in Arm 2 will receive 480 mg nivolumab as a 30-minute (± 5 minutes) IV infusion on Day 1 of each treatment cycle every 4 weeks until progression, unacceptable toxicity, withdrawal of consent, or the subject reaches a maximum of 2 years from the first on-study dose, whichever occurs first. In this arm, each 28-day dosing period will constitute a cycle.

Subjects in Arm 1 may be dosed no less than 12 days from the previous dose; subjects in Arm 2 may be dosed no less than 26 days from the previous dose.

No dose escalations or reductions of nivolumab are allowed. There are no premedications recommended for nivolumab until infusion reactions have been observed in the subject. 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 4.5.5.

Dose delay criteria, criteria to resume treatment, and dose discontinuation criteria can be found in Section 4.5.1, Section 4.5.2, and Section 4.5.3, respectively.

4.5.1 Dose Delay Criteria

Nivolumab administration should be delayed for the following:

- Grade 2 non-skin drug related AEs, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities
- Any Grade 3 skin, drug-related AE
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay
  - Grade ≥ 3 AST, ALT, Total Bilirubin will require dose discontinuation

- Any AE, laboratory abnormality, or intercurrent 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.

4.5.2 Criteria to Resume Treatment

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
- For subjects with Grade 2 AST, ALT and/or Total Bilirubin Abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the Medical Monitor or designee.

Subjects with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor (or designee). Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

Dose interruption of nivolumab which results in treatment interruption of > 6 weeks require treatment discontinuation, with exceptions as noted in Section 4.5.3. There will be no dose reductions for nivolumab.

4.5.3 Dose Discontinuation Criteria

Nivolumab treatment should be permanently discontinued for the following:

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

- ♦ Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
- ♦ Grade ≥ 3 drug-related AST, ALT or Total Bilirubin requires discontinuation*
- ♦ Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN

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

- Any Grade 4 drug-related AE or laboratory abnormality, except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 drug-related endocrinopathy AE, such as adrenal insufficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Medical Monitor.
- Any event that leads to interruption in dosing lasting > 6 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
  - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor (or designee).
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.

Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks, the BMS Medical Monitor (or designee) must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

4.5.4 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 is considered an immuno-oncology agent 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 the nivolumab IB and in Appendix 2.

4.5.5 Treatment of Nivolumab-Related Infusion Reactions

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

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

For **Grade 1** 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 administrations.

For **Grade 2** symptoms: (moderate reaction required therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids); prophylactic medications indicated for ≤ 24 hours):

- Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further BMS-936558 will be administered at that visit.
- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg

should be administered at least 30 minutes before nivolumab infusions. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

For **Grade 3 or 4** symptoms: (severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates). Grade 4: Life-threatening; pressor or ventilatory support indicated):

- Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the Investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms.

In case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

4.6 Blinding/Unblinding

Not applicable.

4.7 Treatment Compliance

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

4.8 Destruction of Study Drug

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

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

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

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.

- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

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

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

4.9 Return of Study Drug

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

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

4.10 Retained Samples for Bioavailability / Bioequivalence

Not Applicable.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Procedural Outline (CA209384)

Procedure	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	
Inclusion/Exclusion Criteria	X	
Medical History	X	
Safety Assessments		
Physical Examination	X	Within 28 days prior to first randomized dose[a]
Vital Signs	X	Temperature, BP, HR, RR, O2 saturation by pulse oximetry (at rest preferred). Also monitor amount of supplemental oxygen if applicable. Obtain vital signs at screening visit and within 72 hours of first randomized dose.
ECOG Performance Status	X	Within 28 days prior to first randomized dose[a]
Assessment of Signs and Symptoms	X	After obtaining Informed Consent, assess all signs and symptoms within 14 days of study randomization, prior to study treatment initiation.
Serious Adverse Events Assessment	X	Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures.
Adverse Events Assessment	X	

Table 5.1-1: Screening Procedural Outline (CA209384)

Procedure	Screening Visit	Notes
Laboratory Tests: hematology, chemistry, liver function tests, thyroid function tests, and hepatitis B and C markers	X	EGFR mutations status should be documented if available. Labs performed locally within 14 days prior to randomization: Hematology includes WBC with differential, ANC, lymphocyte count, hemoglobin, hematocrit, and platelet count. Chemistry includes BUN or urea level, creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, glucose, and LDH. Liver function test includes aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase (ALP), and albumin. Thyroid function test includes TSH, free T3 and free T4. Hepatitis B surface antigen (HBsAg) and hepatitis C antibody (HCV Ab) should also be collected within 28 days prior to randomization. All results should be available prior to dosing.
Review of Concomitant Medications	X	Within 14 days prior to first randomized dose[a]
Pregnancy Test (WOCBP only)	X	Serum or urine pregnancy test to be performed locally within 24 hours prior to first randomized dose.
Efficacy Assessments		
Tumor Assessments	X	MRI of brain (with contrast, unless contraindicated) is required in subjects with a known history of treated brain metastases. [a] CT/MRI of chest, abdomen, pelvis, and all known sites of disease as clinically indicated should be imaged at the screening visit. All screening tumor assessments must be done within 28 days of first randomized dose.
Outcome Assessments		
EQ-5D-3L	X	
Study Drug		
Randomize	X	

ANC, absolute neutrophil count; ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; BP, blood pressure; BUN, blood urea nitrogen; CNS, central nervous system; EGFR, epidermal growth factor receptors; HBsAg, Hepatitis B surface antigen; HCV ab, Hepatitis C antibody; HR,

heart rate; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; O2, oxygen; RR respiratory rate; WBC, white blood cell.

[a] Subjects may continue with the pre-study nivolumab treatment during the screening assessments.

Table 5.1-2: On-Treatment Assessments (CA209384)

Procedure[a]	Every Cycle (± 2 days)	Every 4 Weeks (± 2 days)	Every 6 Weeks (± 2 days)	Every 8 Weeks (± 2 days)	Every 6 Months (± 2 days)	End of Treatment	Notes
Safety Assessments							
Physical Examination	X						
Vital Signs	X					X	Within 72 hours prior to dosing and at EOT. Include temperature, BP, HR, RR, O2 saturation by pulse oximetry (at rest preferred) prior to dosing and at any time there are new or worsening respiratory symptoms.
ECOG PS	X						Within 72 hours prior to each dose
Assessment of Signs and Symptoms	X						
Serious Adverse Event Assessment	X						Assessed using NCI CTCAE v. 4.0
Adverse Events Assessment	X						Assessed using NCI CTCAE v. 4.0
Laboratory Tests: hematology tests	X						Includes WBC count with differential, ANC, lymphocyte count, hemoglobin, hematocrit, and platelet count. Results should be available prior to dosing.
Laboratory Tests: chemistry tests	X						Chemistry (BUN or urea, creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, and glucose), LDH. Results should be available prior to dosing.
Laboratory Tests: liver function test	X						Includes AST, ALT, total bilirubin, alkaline phosphatase, albumin. Completed within 72 hours of dosing. Results should be available prior to dosing.

Table 5.1-2: On-Treatment Assessments (CA209384)

Procedure[a]	Every Cycle (± 2 days)	Every 4 Weeks (± 2 days)	Every 6 Weeks (± 2 days)	Every 8 Weeks (± 2 days)	Every 6 Months (± 2 days)	End of Treatment	Notes
Laboratory Tests: thyroid function test			X[b]	X[c]		X	TSH should be evaluated every 3 cycles (6 weeks) in Arm 1 and every 2 cycles (8 weeks) in Arm 2 and EOT. However, reflexive free T3 and free T4 should be performed if TSH is abnormal. Results should be available prior to dosing.
Pregnancy Test (WOCBP only)		X					Serum or urine pregnancy test to be performed locally within 24 hours prior dosing.
Review of Concomitant Medication	X						
Efficacy Assessments							
Tumor Assessments				X			Tumor assessment should be performed every 8 weeks (±1 week) for the first year of the study, then every 3 months for the second year of the study, followed by the local standard of care afterwards. Recommended to include chest, abdomen, pelvis, and all known sites of disease as clinically indicated. Use same imaging method as was used at screening/baseline. Subjects with a history of brain metastasis should have surveillance MRI approximately every 8 weeks for the first year of the study, or sooner if clinically indicated, then every 3 months for the second year of the study, followed by local standard of care afterwards.
Survival Status	X						

Table 5.1-2: On-Treatment Assessments (CA209384)

Procedure[a]	Every Cycle (± 2 days)	Every 4 Weeks (± 2 days)	Every 6 Weeks (± 2 days)	Every 8 Weeks (± 2 days)	Every 6 Months (± 2 days)	End of Treatment	Notes
Outcomes Research Assessment							
EQ-5D-3L					X		Should be completed prior to dosing.
Pharmacokinetic (PK) and Immunogenicity Assessment							
PK samples	See Section 5.5 and Table 5.5.1-1 and Table 5.5.1-2.						
Immunogenicity samples	See Section 5.5 and Table 5.5.1-1 and Table 5.5.1-2						
Study Drug							
Dispense Study Drug	X						

ALT, alanine aminotransferase; ALP, alkaline phosphatase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; BP, Blood pressure; BUN, blood urea nitrogen; CTCAE, Common Terminology Criteria for Adverse Events; EOT, end of treatment; HR, heart rate, LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; NCI, National Cancer Institute; PK, pharmacokinetic; O2, oxygen; RR, respiratory rate; TSH, thyroid stimulating hormone; WBC, white blood cell; WOCBP, women of childbearing potential.

[a] Assessments should start at Cycle 1 unless otherwise noted.

[b] Thyroid function tests should be performed every 6 weeks (every 3 cycles) for subjects in Arm 1 only.

[c] Thyroid function tests should be performed every 8 weeks (every 2 cycles) for subjects in Arm 2 only.

Table 5.1-3: Off-Treatment Follow-Up Assessments (CA209384)

Procedure	Follow-up Visits 1 (XO1) and 2 (XO2) XO1 to occur approximately 30 days ± 5 days after last dose or coinciding with the date of discontinuation if the date of discontinuation (± 5 days) is greater than 35 days after the last dose. XO2 to occur approximately 70 days after XO1 (± 5 days)	Further Follow-Up Every 6 months (±1 month) after Follow-Up Visit 2 for up to 3 years	Notes
Safety Assessments			
Physical Examination	X		
Vital Signs	X		Temperature, BP, HR, RR, O2 saturation by pulse oximetry (at rest preferred). Also monitor amount of supplemental oxygen if applicable.
ECOG PS	X		
Assessment of Signs and Symptoms	X		
Serious Adverse Events Assessment	X		Assessed using NCI CTCAE v. 4.0
Adverse Events Assessment	X		Assessed using NCI CTCAE v. 4.0
Laboratory Tests: hematology tests	X		Should be done at Follow-Up Visit 2 if results were abnormal at Follow-Up Visit 1. Includes WBC count with differential, ANC, lymphocyte count, hemoglobin, hematocrit, and platelet count.
Laboratory Tests: chemistry tests	X		Should be done at Follow-Up Visit 2 if results were abnormal at Follow-Up Visit 1. Chemistry (BUN or urea, creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, and glucose), LDH.

Table 5.1-3: Off-Treatment Follow-Up Assessments (CA209384)

Procedure	Follow-up Visits 1 (XO1) and 2 (XO2) XO1 to occur approximately 30 days ± 5 days after last dose or coinciding with the date of discontinuation if the date of discontinuation (± 5 days) is greater than 35 days after the last dose. XO2 to occur approximately 70 days after XO1 (± 5 days)	Further Follow-Up Every 6 months (±1 month) after Follow-Up Visit 2 for up to 3 years	Notes
Laboratory Tests: liver function tests	X		Should be done at Follow-Up Visit 2 if results were abnormal at Follow-Up Visit 1. Includes AST, ALT, total bilirubin, ALP, albumin.
Laboratory Tests: thyroid function tests	X		Should be done at Follow-Up Visit 2 if results were abnormal at Follow-Up Visit 1. Reflexive free T3 and free T4 should be performed if TSH is abnormal.
Pregnancy Test (WOCBP only)	X		Serum or urine pregnancy test to be performed locally.

Table 5.1-3: Off-Treatment Follow-Up Assessments (CA209384)

Procedure	Follow-up Visits 1 (XO1) and 2 (XO2) XO1 to occur approximately 30 days ± 5 days after last dose or coinciding with the date of discontinuation if the date of discontinuation (± 5 days) is greater than 35 days after the last dose. XO2 to occur approximately 70 days after XO1 (± 5 days)	Further Follow-Up Every 6 months (±1 month) after Follow-Up Visit 2 for up to 3 years	Notes
Efficacy Assessments			
Tumor Scans	See notes		For subjects without documented progression per RECIST 1.1, tumor assessment should continue to be performed every 8 weeks (±1 week) for the first year of the study, then every 3 months for the second year of the study, followed by the local standard of care afterwards. Recommended to include chest, abdomen, pelvis, and all known sites of disease as clinically indicated. Use same imaging method as was used at screening/baseline. Subjects with a history of brain metastasis should have surveillance MRI approximately every 8 weeks for the first year of the study, or sooner if clinically indicated, then every 3 months for the second year of the study, followed by local standard of care afterwards.
Subject Survival Status	X	X	Phone call or e-mail are acceptable if a clinical visit is not otherwise needed. Ad hoc data collection may be performed as needed.

Table 5.1-3: Off-Treatment Follow-Up Assessments (CA209384)

Procedure	Follow-up Visits 1 (XO1) and 2 (XO2) XO1 to occur approximately 30 days ± 5 days after last dose or coinciding with the date of discontinuation if the date of discontinuation (± 5 days) is greater than 35 days after the last dose. XO2 to occur approximately 70 days after XO1 (± 5 days)	Further Follow-Up Every 6 months (±1 month) after Follow-Up Visit 2 for up to 3 years	Notes
Outcomes Assessments			
EQ-5D-3L	X	X	Can be conducted via a telephone call if an in-person clinical visit is not otherwise needed.

ALT, alanine aminotransferase; ALP, alkaline phosphatase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; BP, blood pressure; CTCAE, Common Terminology Criteria for Adverse Events; HR, heart rate; RR respiratory rate; NCI, National Cancer Institute; O2, oxygen; TSH, thyroid stimulating hormone; WBC, white blood count; WOCBP, women of childbearing potential.

5.1.1 Retesting During Screening or Lead-in Period

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

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

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

5.2 Study Materials

The site will provide:

- All required materials for the tests performed locally (ie, relevant to clinical laboratory tests)
- A well-calibrated scale for recording body weight
- A calibrated sphygmomanometer
- Thermometer for temperature
- A validated temperature-controlled refrigerator
- All materials required for accurate source documentation of study activities including the EQ-5D-3L.

BMS will provide:

- A BMS-approved protocol and any amendments or administrative letters (if required)
- Case report forms (electronic or hard copy)
- Nivolumab
- BMS-936558 (nivolumab) IB
- IWRS manual
- Laboratory manuals for collection and handling of blood (including PK and immunogenicity)
- Site manual including
  - RECIST 1.1 pocket guide
  - NCI CTCAE V4.0

5.3 Safety Assessments

Safety assessments will be conducted throughout the trial and during 100 days after the last dose of study treatment as described in Table 5.1-2 and Table 5.1-3. The assessments described in Table 5.1-2 should be monitored starting on Cycle 1 Day 1 (unless otherwise noted in the table) until discontinuation from study therapy.

Only data for the procedures and assessments specified in this protocol should be submitted to BMS on a case report form. Additional procedures and assessments may be performed as part of standard of care; however, data for these assessments should remain in the patient's medical record and should not be provided to BMS unless specifically requested. NCI CTCAE version 4.0 will be the criteria used to assess severity of AEs.

5.3.1 Imaging Assessment for the Study

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the Study Investigator as per standard medical/clinical judgment.

5.4 Efficacy Assessments

Study evaluations will take place in accordance with Table 5.1-2 and should be performed, starting with Cycle 1 Day 1, according to RECIST 1.1 criteria (Appendix 1).

High resolution CT with oral or IV contrast or contrast-enhanced MRI are the preferred imaging modalities for assessing radiographic tumor response. If a subject has a known allergy to contrast material, please use local prophylaxis standards to obtain the assessment with contrast if at all possible or use an alternate modality. In cases where contrast is strictly contraindicated, a non-contrast scan will suffice. Screening assessments, including chest, abdomen, pelvis, brain, and all known or suspected sites of disease as clinically indicated, should be performed within 28 days of first dose of study drug. Brain MRI is the preferred imaging method when evaluating CNS metastasis is necessary. In addition to chest and abdomen, all known or suspected sites of disease (including CNS) should be assessed at subsequent assessments using the same imaging method and technique. If more than one method is used at screening, then the most accurate method according to RECIST 1.1 should be used when recording data and should again be used for all subsequent assessments. Bone scan, PET scan, or ultrasound is not adequate for assessment of RECIST response. In selected circumstances where such modalities are the sole modality used to assess certain non-target organs, those non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in the target disease or when progression in bone is suspected. Previously treated CNS metastases are not considered measurable lesions for purposes of RECIST determined response.

Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible. Changes in tumor measurements and tumor responses to guide ongoing study treatment decisions should be assessed by the investigator using RECIST 1.1.

5.5 Pharmacokinetic Assessments

Samples for PK and immunogenicity assessments will be collected for all subjects receiving nivolumab as described in Table 5.5.1-1 and Table 5.5.1-2. 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 evaluation is provided in Table 5.5.1-1 and Table 5.5.1-2. PK samples will be analyzed for nivolumab by a validated immunoassay. Immunogenicity samples will be analyzed for anti-nivolumab antibodies by a validated immunogenicity assay; samples may also be analyzed for neutralizing 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 assessments may also be used for immunogenicity analysis if required (eg, insufficient volume for complete immunogenicity assessment or to follow up on suspected immunogenicity related AE).

Table 5.5.1-1: Pharmacokinetic and Immunogenicity Sample Collection for Nivolumab - Arm 1

Study Day 1 cycle = 2 weeks	Sampling Event (Relative To Time of Infusion) Hour[a]	Time (Relative To Start of Infusion) Hour: Min[a]	Pharmacokinetic Blood Sample for Nivolumab	Immunogenicity Blood Sample for Nivolumab
C1D1	0 (Predose)	00:00	X	X
C3D1	0 (Predose)	00:00	X	X
C8D1	0 (Predose)	00:00	X	X
Every 8th Cycle after C8D1 for up to 2 years of treatment	0 (Predose)	00:00	X	X

[a]Predose sample may be collected up to 3 hours prior to the start of infusion. If it is known that a dose is going to be delayed, then the 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 and Immunogenicity Sample Collection for Nivolumab- Arm 2

Study Day 1 cycle = 4 weeks	Sampling Event (Relative to Time of Infusion) Hour[a]	Time (Relative to Start of Infusion) Hour: Min[a]	Pharmacokinetic Blood Sample for Nivolumab	Immunogenicity Blood Sample for Nivolumab
C1D1	0 (Predose)	00:00	X	X
C2D1	0 (Predose)	00:00	X	X
C4D1	0 (Predose)	00:00	X	X
Every 4th cycle after C4D1 for up to 2 years of treatment	0 (Predose)	00:00	X	X

[a] Predose sample may be collected up to 3 hours prior to the start of the infusion. If it is known that a dose is going to be delayed, then the 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

Not applicable.

5.7 Outcomes Research Assessments

The EQ-5D-3L comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety) and a visual analog rating scale. The responses to the EQ-5D-3L domains will be converted to health status index based on the European scoring algorithm.

5.8 Other Assessments

Not applicable.

6 ADVERSE EVENTS

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

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

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

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

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

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

Suspected Unexpected Serious Adverse Reaction is a serious adverse event that is both unexpected and related to an IMP or comparator IMP, for which expedited reporting to clinical investigators, Ethics Committees and Health Authorities is required (Previously known as ESR).

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

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

6.1 Serious Adverse Events

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

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

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

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

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

NOTE:

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

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent

- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

6.1.1 Serious Adverse Event Collection and Reporting

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

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

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

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

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours of awareness of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

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

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

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

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

6.2.1 Nonserious Adverse Event Collection and Reporting

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

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

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

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

6.3 Laboratory Test Result Abnormalities

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

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

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

6.4 Pregnancy

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

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

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 subject should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 Overdose

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

6.6 Potential Drug Induced Liver Injury (DILI)

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

Potential drug induced liver injury is defined as:

1. AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

   AND

2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

   AND

3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

6.7 Other Safety Considerations

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

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

A Data Monitoring Committee (DMC) will be utilized to provide general oversight, safety, and efficacy (including assessment of 6 month PFS co-primary endpoint) considerations for this study. 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 therapy. The DMC will act in an advisory capacity to BMS and will monitor subject safety data for the study approximately every 12 months or more frequently if deemed necessary for the duration of the trial.

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.

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

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

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

The primary analyses evaluate the non-inferiority of post-randomization 6-month and 12-month milestone PFS rate of nivolumab 480 mg Q4W vs the PFS rate of nivolumab 240 mg Q2W in subjects with disease control (CR/PR/SD) confirmed on 2 consecutive tumor assessments and after receiving up to 12 months (52 weeks) of nivolumab 3 mg/kg or 240 mg Q2W treatment. The non-inferiority margin of -10% was chosen for this study. Patients who received nivolumab for up to 12 months (52 weeks) and achieved CR, PR, or SD confirmed by 2 tumor assessments will be randomized. It is estimated that the 12-month milestone PFS rate post-randomization is 0.48 with 240 mg Q2W and 6-month PFS rate post-randomization is 0.63.

The sample size was computed based on a cumulative hazard function which accounts for both progression and censoring distributions. Using cumulative hazard function and its relation with survival function, it is estimated that approximately 620 patients, 310 in each arm, will provide 80% power for the lower bound of a 95.2% one-sided confidence interval above -10% at the 12-month milestone and the lower bound of a 99.3% confidence interval above -10% at 6 months

if PFS rates of the 2 arms are assumed to be equal. The experiment-wise error rate is maintained at one-sided 5% level.

To account for those who are randomized but not receiving treatment, 320 per arm will be randomized. With a 15% screen failure rate, approximately 753 subjects will be screened to achieve approximately 640 randomized subjects.

UPDATE as of revised protocol 05: Due to early stop of enrollment of the study, the sample size will be the number of subjects randomized after enrolment stops. Approximately 350 subjects are expected to be randomized and receive study treatment. With the significant reduction of sample size, there is insufficient power to demonstrate non-inferiority of the two treatment regimens. Hence, the adjustment of alpha between 6 months and 12 months PFS rates (as originally planned) will not be conducted. Instead, 95% one-sided confidence interval around the difference of PFS rates will be generated.

8.2 Populations for Analyses

- All enrolled subjects: all subjects who signed an informed consent form and were registered into the IWRS.
- All randomized subjects: all subjects who are randomized to 240 mg every 2 weeks or 480 mg every 4 weeks. This is the primary population for efficacy analyses. Subpopulation analyses will be conducted by tumor histology (Sq or non-Sq) and response at randomization (PR or CR vs SD).
- All treated subjects: all randomized subjects who received at least 1 dose of nivolumab. This is the primary population for safety analyses. Subpopulation analyses will be conducted by tumor histology and response at randomization for some safety variables.
- PK and immunogenicity subjects: all treated subjects with available serum time-concentration data.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

The co-primary objectives of this trial will be assessed by PFS rate at 6 months after randomization and PFS rate at 1 year after randomization. PFS is defined as the time from the date of randomization to the date of first documented tumor progression determined by the investigator or death, whichever is earlier. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on-study tumor assessments and did not die will be censored on the first dosing date. Subjects who received any subsequent anti-cancer therapy (including on-treatment palliative radiation therapy of non-target bone lesions or CNS lesions) without a prior reported progression will be censored at the last evaluable tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy.

8.3.2 Secondary Endpoint(s)

Secondary objectives will be assessed by:

- PFS rate at 1 year after randomization by tumor histology and by response criteria
- PFS rate at 2 years after randomization

- OS rate at 1 year and OS up to 3 years by arm, histology, and response status at randomization. OS is defined as time from the date of randomization to the date of death. Subjects who did not die by the end of the study will be censored at the last known date alive. OS rate at 1 year is the rate from KM estimated at one year after randomization.
- Safety and tolerability of nivolumab, as measured by incidence and severity of AEs and specific laboratory abnormalities

8.3.3 Exploratory Endpoint(s)

Exploratory objective will be assessed by

- Relationship of pharmacokinetics and immunogenicity of nivolumab with respect to selected safety and efficacy endpoints at 240 mg Q2W and 480 mg Q4W
- EQ-5D-3L
- Other exploratory endpoints are discussed in detail in the statistical analysis plan

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Demographics and baseline disease characteristics including age, sex, race, ethnicity, weight, baseline disease diagnosis, and medical condition will be summarized using descriptive statistics by dose regimen.

8.4.2 Efficacy Analyses

PFS will be summarized by KM product-limit method and confidence interval for hazard ratio will be produced from a stratified (by tumor histology and response category) proportional hazard model. Median values of PFS, along with one-sided 95% CI using the Brookmeyer and Crowley method, will be calculated. The status of subjects who are censored in the PFS KM analysis will be tabulated for each dose regimen.

The 95% one-sided confidence intervals, adjusted for stratifying factors, for PFS rates at 6 months and 12 months will be calculated for each dose regimen and difference between dose regimens using the Greenwood formula.

OS and OS rates at 6 months and 12 months will be analyzed using the same method as for PFS and PFS rates.

8.4.3 Safety Analyses

Safety will be analyzed through the incidence of deaths, AEs, SAEs, AEs leading to discontinuation, AEs leading to dose interruption, select AEs, and specific laboratory abnormalities (worst grade) in each arm. Toxicities will be graded using the NCI CTCAE version 4.0.

8.4.4 Pharmacokinetic Analyses

The nivolumab serum concentration data from this study may be combined with data from other nivolumab studies in the population pharmacokinetic model. These models may be used to evaluate the effects of intrinsic and extrinsic covariates on the pharmacokinetics of nivolumab

and to determine measures of individual exposure. In addition, model determined exposures may be used for exposure-response analyses. Results of population pharmacokinetics and exposure-response analyses will be reported separately.

8.4.5 Biomarker Analyses

Not applicable.

8.4.6 Outcomes Research Analyses

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

Subject's overall health state on an EQ-VAS at each assessment time point as well as change from baseline will be summarized using descriptive statistics by arm (including mean and 95% confidence interval), as randomized.

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

Summary statistics will be calculated for the population preference-based health state utility score (EQ-5D-3L Index) at each assessment as well as patients' change from baseline at each assessment by treatment arm, as randomized.

8.4.7 Other Analyses

Methodology for exploratory analyses including immunogenicity is described in the statistical analysis plan.

8.5 Interim Analyses

In addition to the interim analyses specified in Section 7, additional interim analyses may be conducted to address regulatory questions or requests, for example.

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 and Regulatory Authority(ies), if required by local regulations, approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

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

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

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

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

9.1.2 Monitoring

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

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

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

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

9.1.2.1 Source Documentation

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

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a

copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

9.1.3 Investigational Site Training

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

9.2 Records

9.2.1 Records Retention

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

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

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

9.2.2 Study Drug Records

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

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- nonstudy disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to BMS
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

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

9.2.3 Case Report Forms

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

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used. 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, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

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

9.3 Clinical Study Report and Publications

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

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

- Study Steering Committee chair or their designee

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

10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (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. Women must continue to have pregnancy tests. Acceptable alternate methods of highly or less effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

11 LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
ALK	Anaplastic lymphoma kinase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AT	aminotransaminases
BMS	Bristol-Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CNS	Central nervous system
CRF	Case Report Form, paper or electronic
CR	Complete response
CrCl	Creatinine clearance
CTCAE	Common Terminology Criteria for Adverse Events
DILI	Drug-induced liver injury
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EGFR	Epidermal growth factor receptors
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
HIV	Human Immunodeficiency Virus
HR	heart rate
HRT	hormone replacement therapy
ICH	International Conference on Harmonisation
IB	Investigator Brochure

Term	Definition
ie	id est (that is)
IEC	Independent Ethics Committee
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
IO	Immuno-oncology
IP	Investigational Product
IRB	Institutional Review Board
IV	intravenous
IWRS	Interactive web-based response system
kg	kilogram
Km	Kaplan-Meier
L	liter
LFT	Liver function test
mg	milligram
mL	milliliter
mmHg	millimeters of mercury
N	number of subjects or observations
N/A	not applicable
NCI	National Cancer Institute
NIMP	non-investigational medicinal products
Non-Sq	Non-squamous
NSCLC	Non-small cell lung cancer
OS	Overall survival
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
PS	Performance status
Q2W	Every 2 weeks
Q4W	Every 4 weeks
RECIST	Response Evaluation Criteria in Solid Tumors

Term	Definition
RBC	red blood cell
SAE	serious adverse event
SD	Stable disease
SQ	Squamous
TKI	Tyrosine kinase inhibitors
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
VAS	Visual analog scale
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential

12 REFERENCES

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3 Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol. 2004; 22: 2184-2191.

4 Forbes SA, Bharma G, Bamford S, et al. The catalogue of somatic mutations in cancer (COSMIS). Curr Protoc Hum Genet. 2008; Ch.10: unit 10.11.

5 Amos SM, Duong CP, Westwood JA, et al. Autoimmunity associated with immunotherapy of cancer. Blood. 2011;118:499-509.

6 Brahmer J, Reckamp KL, Baas P, at al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer. N Engl J Med. 2015;373:123-35.

7 Paz-Ares L, Horn L, Borghaei H, et al. Phase III, Randomized Trial (CheckMate 057) of Nivolumab versus Docetaxel in Advanced Non-squamous (non-SQ) Cell Non-small Cell Lung Cancer (NSCLC). Presented at the 2015 Annual Meeting of the American Society of Clinical Oncologist, May 29-June 2, 2015, Chicago, Il.

8 Anti-PD1 (Nivolumab) Investigator Brochure, Bristol-Myers Squibb Research and Development, Princeton, NJ. Version 14. June 2015.Document Control No.: 930038243.

9 CA209017 Final Study Report. An Open-label Randomized Phase III Trial of BMS-936558 (nivolumab) versus Docetaxel in Previously Treated Advanced or Metastatic Squamous Cell Non-small Cell Lung Cancer (NSCLC). Bristol-Myers Squibb Research and Development. Princeton, NJ. February 2015.

10 CA209057 Final Study Report. An Open-label Randomized Phase III Trial of BMS-936558 (nivolumab) versus Docetaxel in Previously Treated Metastatic Non-Squamous Non-small Cell Lung Cancer (NSCLC). Bristol-Myers Squibb Research and Development. Princeton, NJ. May 2015.

APPENDIX 1 RECIST 1.1 CRITERIA

This Appendix has been excerpted from the full RECIST 1.1 criteria. For information pertaining to RECIST 1.1 criteria not contained in the study protocol or in this Appendix, please refer to the full publication.[1]

1 ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

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

1.1 Measurability of tumor

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

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

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

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

Special considerations regarding lesion measurability

Bone lesions:

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

Cystic lesions:

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

Lesions with prior local treatment:

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

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

1.2 Method of assessment

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3 TUMOR RESPONSE EVALUATION AND RESPONSE CRITERIA

3.1 Evaluation of target lesions

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

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

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

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

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

Special notes on the assessment of target lesions

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

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

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

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

3.2 Evaluation of non-target lesions

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

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

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

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

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

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

3.3 New lesions

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

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

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

3.4 Tumor markers

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

4 EVALUATION OF BEST OVERALL RESPONSE

4.1 Time point response

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

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

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

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

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

4.2 Missing assessments and inevaluable designation

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

4.3 Best overall response: all timepoints

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

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

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

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

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

4.4 Special notes on response assessment

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

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

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

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

5 ADDITIONAL CONSIDERATIONS

5.1 Duration of response

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

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

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

5.2 Lesions that disappear and reappear

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

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

5.3 Use of FDG-PET

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

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

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

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

6 REFERENCE

[1] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009; 45:228-247.

APPENDIX 2 MANAGEMENT ALGORITHMS

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

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

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

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

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

GI Adverse Event Management Algorithm

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

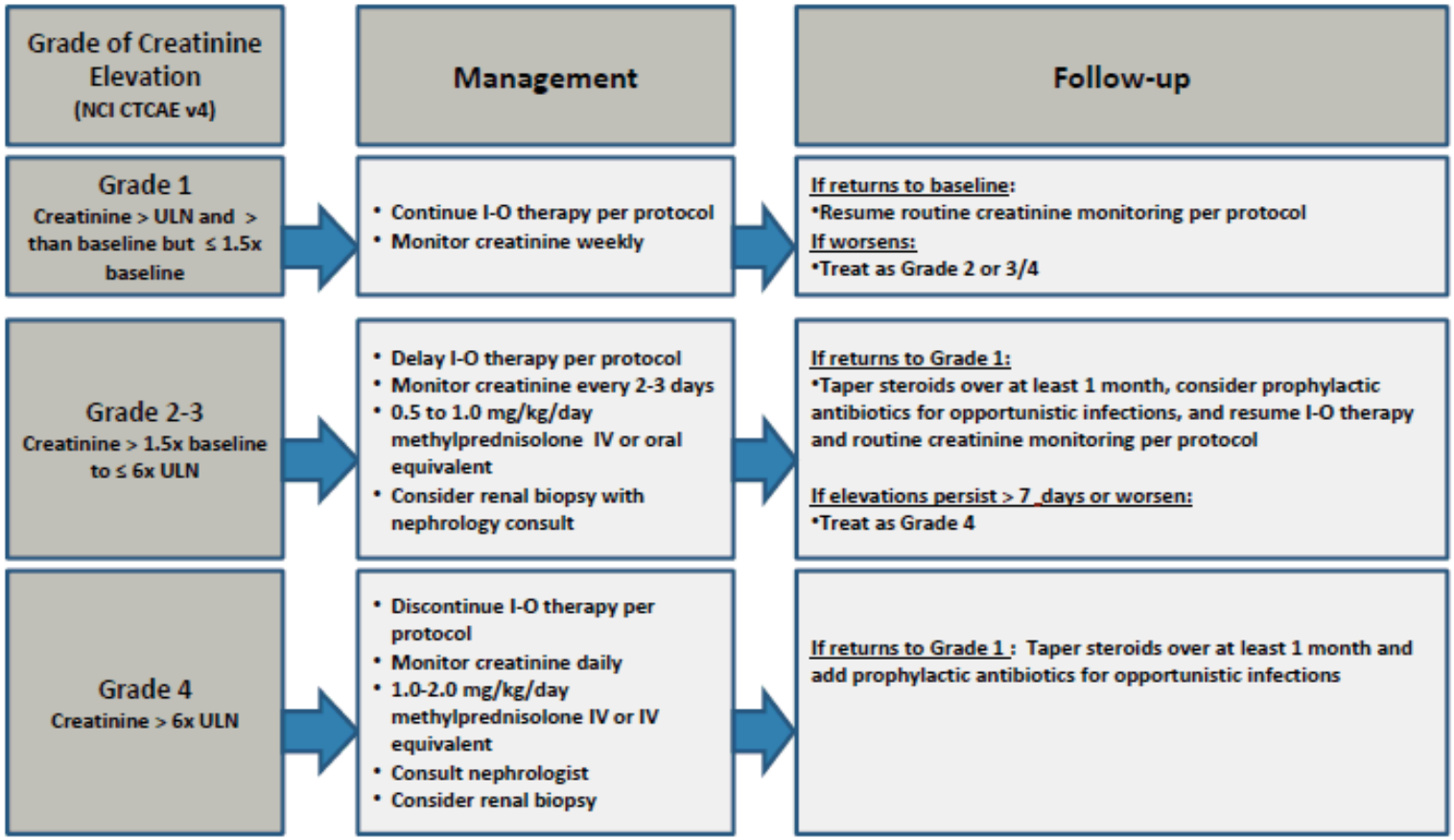
Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat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

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

Updated 05-Jul-2016

Renal Adverse Event Management Algorithm

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

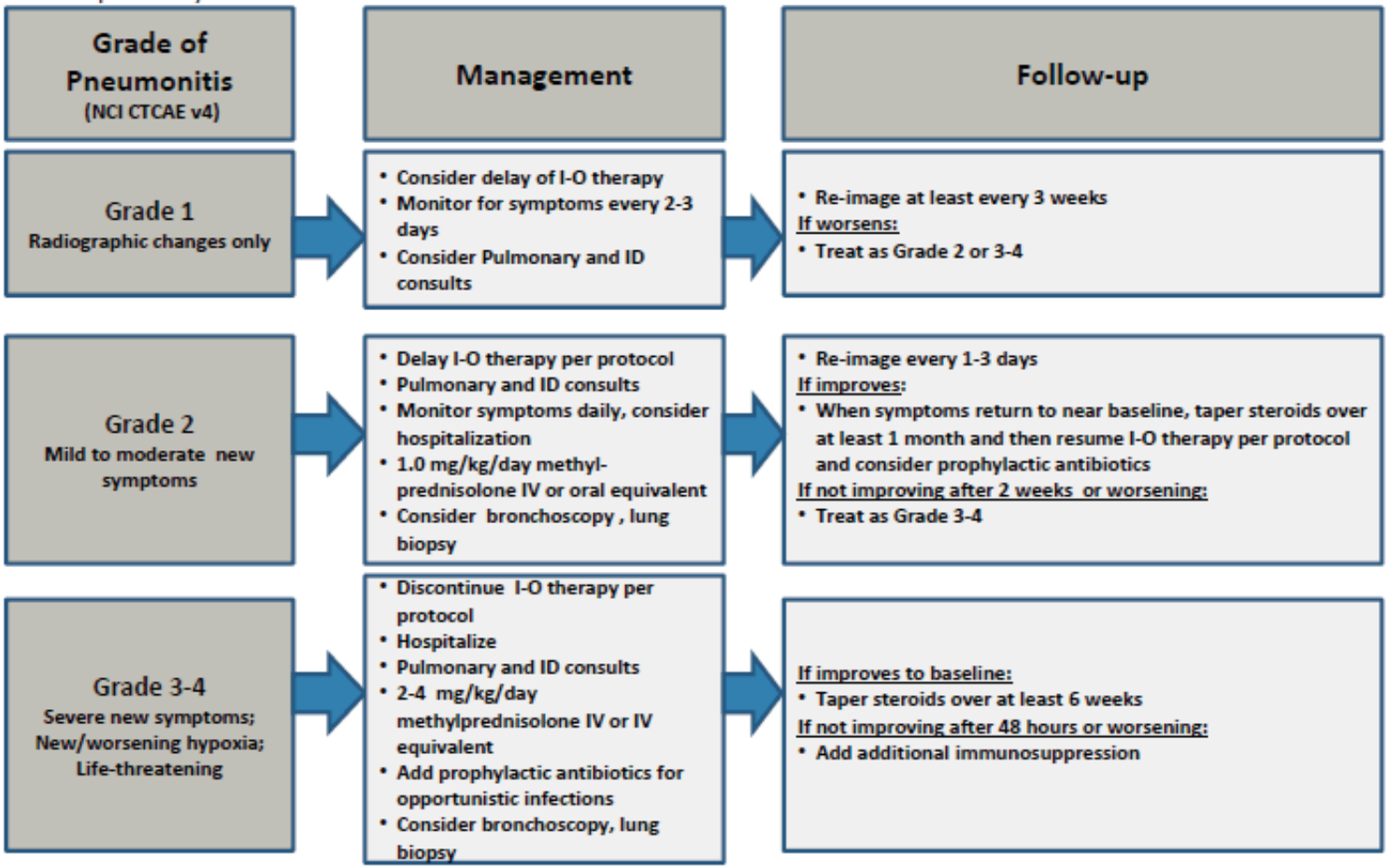


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

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.

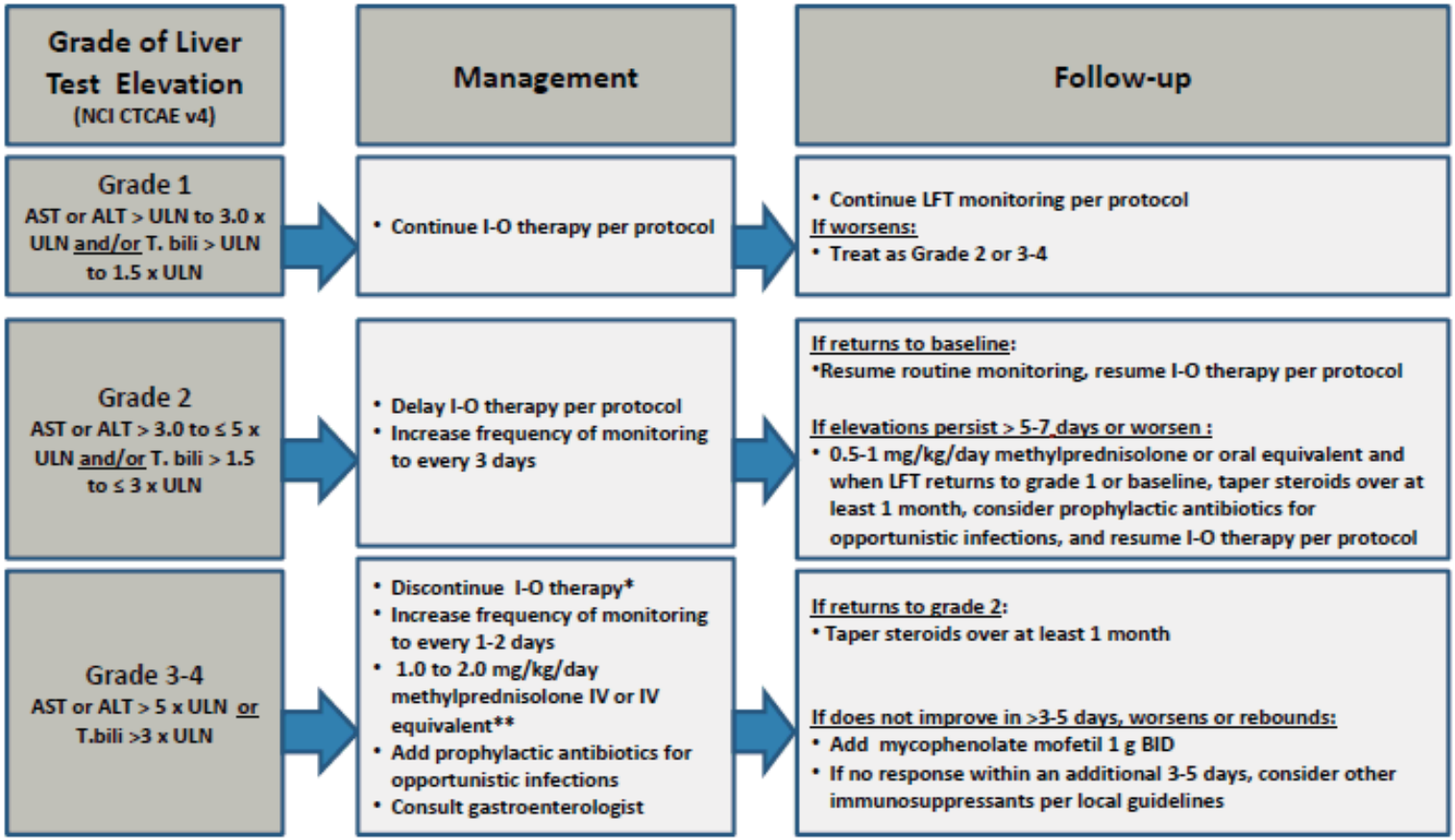


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

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.

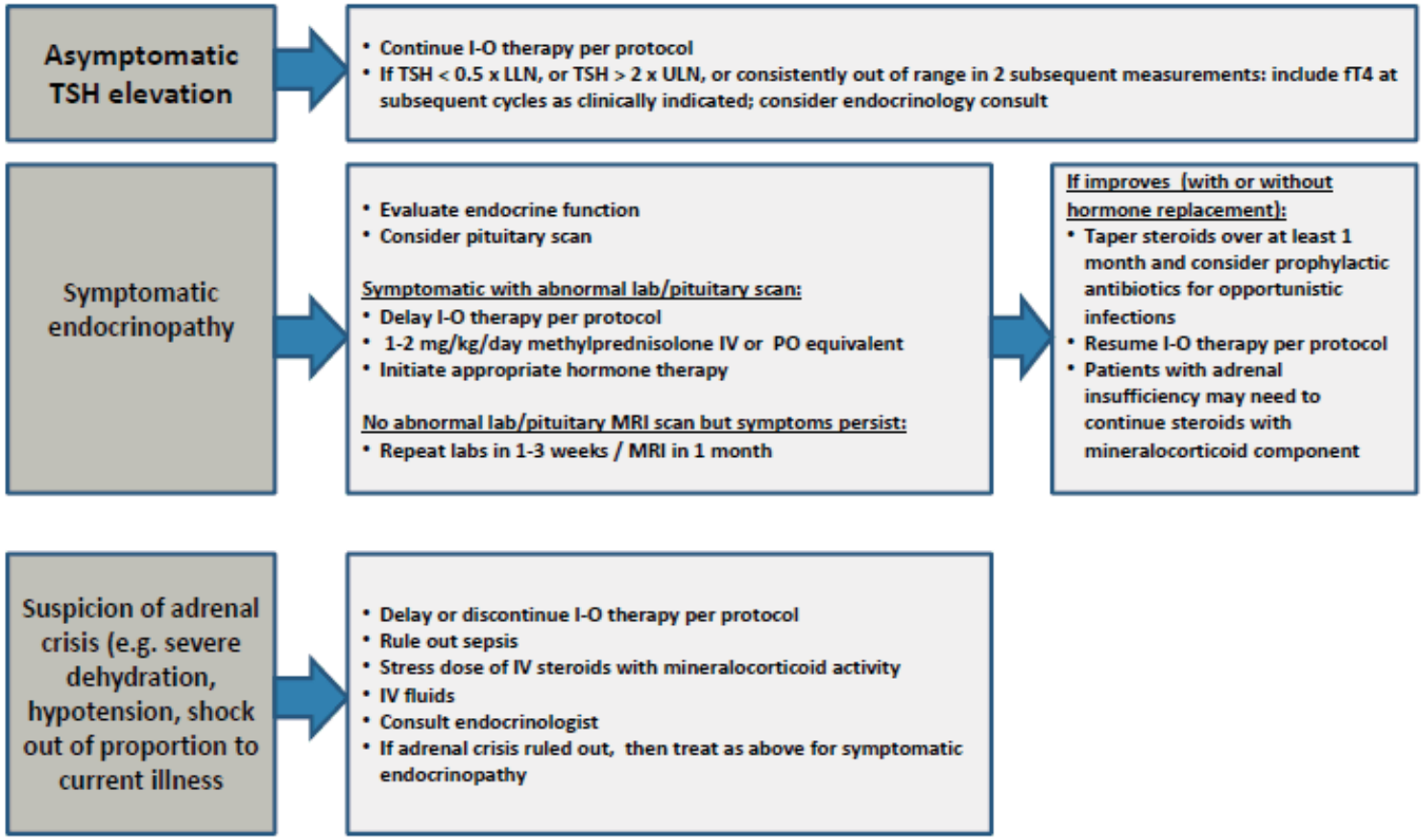
***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**

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

Updated 05-Jul-2016

Endocrinopathy 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.

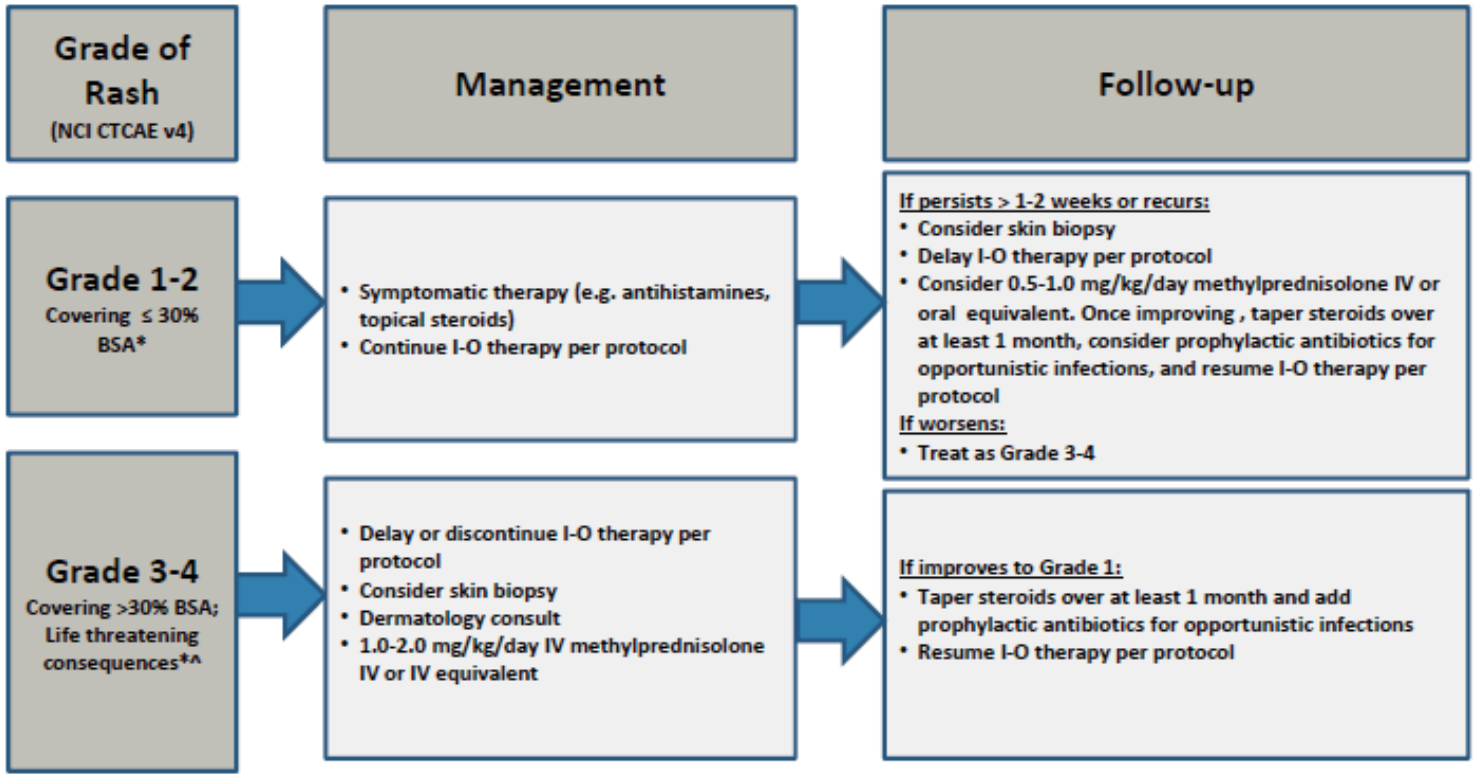


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Skin Adverse Event Management Algorithm

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

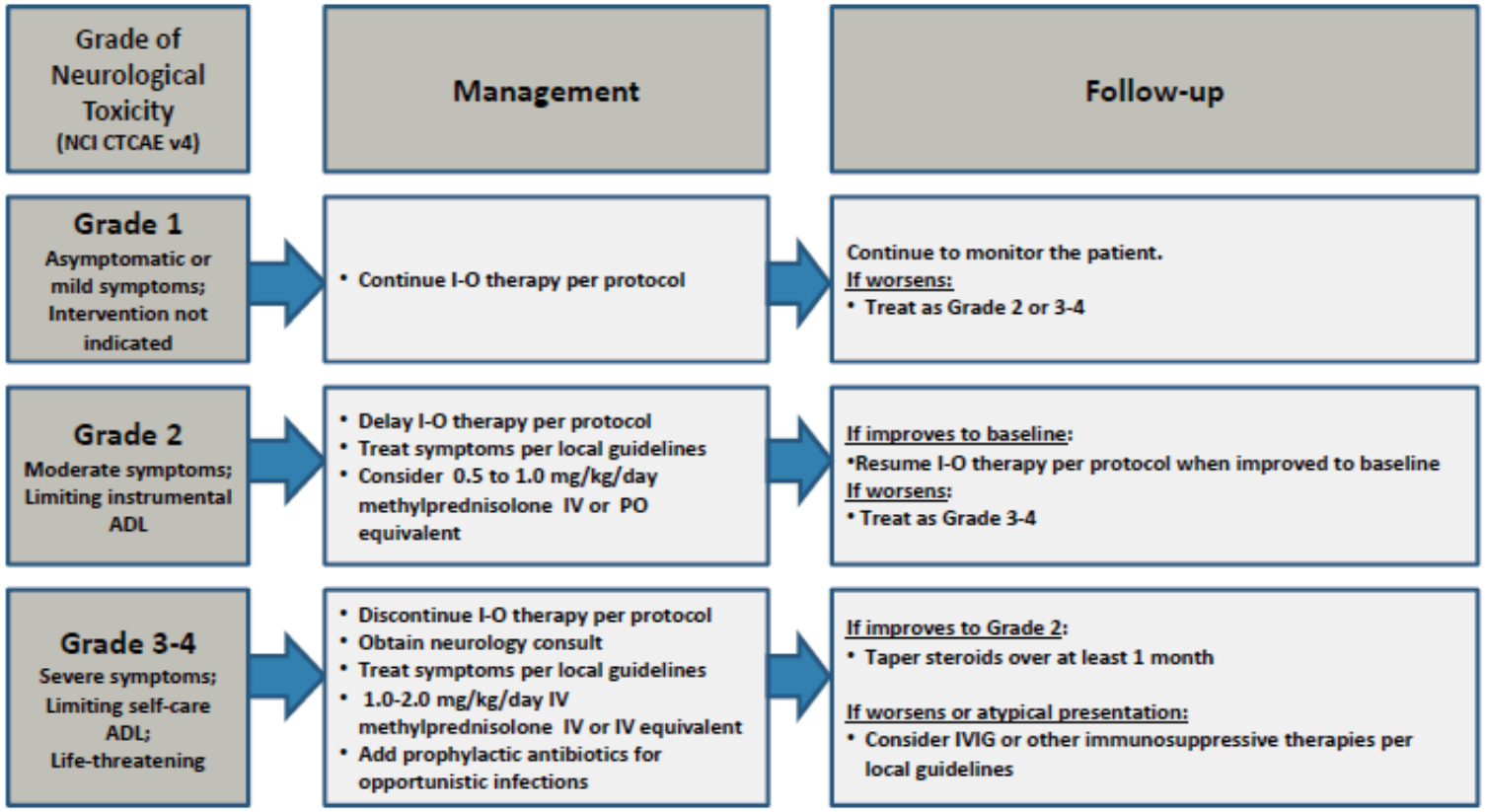


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

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.

Updated 05-Jul-2016

APPENDIX 3 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

- Postmenopausal female
  - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

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

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable

Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b] • Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and intrauterine hormone-releasing system (IUS)[c] • Intrauterine device (IUD)[c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 5. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. [c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Unacceptable Methods of Contraception*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal Sponge with spermicide

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action
- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus).
- Spermicide only
- Lactation amenorrhea method (LAM)

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

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

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

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until end of relevant systemic exposure defined as 7 months after the end of study treatment.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 7 months after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 7 months after the end of study treatment.
- Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of study treatment.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 6.4 and the Section 6 for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting

APPENDIX 4 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for the Revised Protocol 04, 09-Feb-2018

The revised protocol was updated to include additional language for nivolumab program level updates and to add information for interim analyses.

Summary of key changes of Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Study personnel and contact information updated	Study personnel and contact information updated
Section 1.5 Overall Risk/Benefit Assessment	Immune-related adverse events (IMAEs) definitions and management algorithms were added to protocol	IMAEs and management algorithms were added to align with I-O treatment.
Section 3.2 Post Study Access to Therapy	Maximum treatment duration applies to post study access to therapy.	Internal consistency within document
Section 3.3.1 Inclusion Criteria Age and Reproductive Status Appendix 3 Women of Childbearing Potential Definitions and Methods of Contraception	Methods of Contraception were updated and moved to Appendix 3.	Methods of contraception language were updated for safety and to align with nivolumab program level standards.
Section 3.3.2 Exclusion Criteria No. 2 Medical History and Concurrent Diseases Letter k) Section 3.4.1 Prohibited and/or Restricted Treatments	Exclusion/prohibition of treatment with botanical preparations within 2 weeks prior to randomization	Botanical preparations are excluded/prohibited to minimize risks of any interactions with study drugs.
Section 3.3.2 Exclusion Criteria No. 3 Physical and Laboratory Test Findings	Updated exclusion criteria language for hepatitis B virus and hepatitis C virus	Exclusion criteria for hepatitis were updated for clarity and to align with nivolumab program level standards.
Section 3.3.2 Exclusion Criteria No. 4 Allergies and Adverse Drug Reaction	Exclusion of subjects with history of allergy or hypersensitivity to study drug components	Exclusion criteria were updated for safety and to align with nivolumab program level standards.
Section 3.6 Post Study Drug Study Follow up	Language added for the collection of survival status.	Updated for clarity

Summary of key changes of Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 4.5.1 Dose Delay Criteria	Nivolumab dose delay criteria were updated with delays for: • Grade 2 non-skin drug related AEs, with the exception of fatigue • Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities • Any Grade 3 drug-related laboratory abnormality, with the following exceptions: - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay - Grade ≥ 3 AST, ALT, Total Bilirubin will require dose discontinuation	Dose delay criteria were updated for safety and to align with nivolumab program level standards.
Section 4.5.2 Criteria to Resume Treatment	Criteria to resume treatment were updated: • For subjects with Grade 2 AST, ALT and/or Total Bilirubin Abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete. • Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.	Criteria to resume treatment were updated for safety and to align with nivolumab program level standards.
Section 4.5.3 Dose Discontinuation Criteria	Dose discontinuation criteria were updated: • Neurologic toxicity and myocarditis require discontinuation • Adrenal insufficiency requires discontinuation regardless of control with hormone replacement. • Grade ≥ 3 drug-related AST, ALT or Total Bilirubin requires discontinuation	Dose discontinuation criteria were updated for safety and to align with nivolumab program level standards.
Section 6 Adverse Events	Information added on IMAEs. IMAE data collection and adverse event assessment were added.	Information for immune-mediated adverse events was added to align with I-O treatment.
Section 6.2.1 Nonserious Adverse Event Collection and Reporting	Instructions for the collection of nonserious AEs were added.	Instructions were added for safety monitoring.
Section 7 Data Monitoring Committee and Other External Committees	Updated DMC meeting frequency to every 12 months.	Wide experience and established safety management with nivolumab monotherapy. In addition, no safety signal detected from previous interim analyses.
Section 8.5 Interim Analyses	Language added allowing additional interim analyses	Additional interim analyses may be conducted to address regulatory questions or requests, for example.

Summary of key changes of Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Appendix 2 Management Algorithms	Management Algorithms for I-O therapy was added to Appendix 2	Protocol aligns with Investigator Brochure.
Appendix 3 Women of Childbearing Potential Definitions and Methods of Contraception	Appendix 3 Women of Childbearing Potential Definitions and Methods of Contraception added.	Updated contraception language