Official Title of Study:

A Phase IIIb/IV Safety Trial of Flat Dose Nivolumab in Combination with Ipilimumab in Participants with Non-Small Cell Lung Cancer
CheckMate 817, CHECKpoint pathway and nivoluMAb clinical Trial Evaluation

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Clinical Protocol CA209817

A Phase IIIb/IV Safety Trial of Flat Dose Nivolumab in Combination with Ipilimumab in Participants with Non-Small Cell Lung Cancer

CheckMate 817, **CHECK**point pathway and nivolu**MA**b clinical **T**rial **E**valuation

Revised Protocol Number: 06
Incorporates Administrative Letter 08

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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 06	02-Jul-2019	• Removed required number of participants in each special population subgroup • Removed C1D1 physical exam from Table 2-2 • Updated language to clarify that inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent are allowed • Updated treatment after the end of the study language to align with 2 year maximum treatment duration • Added FACT-L collection during survival follow-up, which may be collected in office or over telephone
Administrative Letter 08	02-Oct-2018	Updated Medical Director/Medical Monitor information
Revised Protocol 05	04-Jun-2018	• Revised objectives and endpoints for Cohort C participants • Updated sample size for Cohort C participants • [redacted] • Updated protocol to align with nivolumab program standards
Administrative Letter 07	26-Mar-2018	• Updated study personnel • Corrected errors in wording
Administrative Letter 06	28-Nov-2018	• Corrected numbering Section 6.1.1 Inclusion Criteria for Cohort A1 Special Population
Revised Protocol 04	25-Oct-2017	• Addition of Cohort C participants with high tumor mutation burden with subsequent addition of objectives, endpoints, tissue and blood collection, background, rationale, and analyses. • Palliative radiotherapy language updated • Maximum treatment duration of 24 months added.
Administrative Letter 05	31-Aug-2017	• Updated study personnel and study title
Revised Protocol 03	27-Jul-2017	Revised protocol 03 incorporates language from previous revised protocols, amendments, and administrative letters. These changes include updating the revised protocol with: • Optional special population Cohort A1 • [redacted] • BMS standard days for study follow-up • Change in title to reflect secondary endpoints • New study personnel added Typographical errors were corrected for clarity.
Administrative Letter 04	12-Apr-2017	• Updated study personnel and study title • Clarified metagenomic analyses
Revised Protocol 02	09-Nov-2016	Incorporates Amendment 04
Amendment 04	09-Nov-2016	Added a cohort of 400 participants (Cohort B, second-line non-small cell lung cancer [NSCLC]) who will receive nivolumab plus ipilimumab.

Document	Date of Issue	Summary of Change
		Added specific exclusion criteria for patients with known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) translocations sensitive to available targeted inhibitor therapy.
Revised Protocol 01	15-Sep-2016	Incorporates Amendment 03
Amendment 03	15-Sep-2016	Management algorithms updated per revised nivolumab IB
Original Protocol	22-Jun-2016	Not Applicable

OVERALL RATIONALE FOR THE REVISED PROTOCOL 06

The revised protocol removes the required number of participants in special population subgroups and collects FACT-L during survival follow-up. Additional changes were made to align protocol with program standards.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 06

Section Number & Title	Description of Change	Brief Rationale
Section 5.2.1 All Cohorts (NSCLC	Removed required number of participants for each special population subgroup	Required number of participants for each special population was removed because of limited accrual.
Table 2-2: Treatment Phase Assessments (CA209817)	Removed physical exam at C1D1	Physical exam occurs at screening and does not need to be repeated at C1D1.
Table 2-3: Follow-up and Survival Procedures (CA209817)	FACT-L assessments may be administered in office or over the telephone.	FACT-L may be performed over the phone if office visit is not required for other assessments.
Section 7.7.2 Other Restrictions and Precautions	Updated language to clarify that inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent are allowed.	Language updated to align with current program standards.
Section 7.8 Treatment After the End of the Study	Updated treatment after the end of the study	Updated treatment after the end of the study to align language with 2 year maximum treatment duration
Table 2-3: Follow-up and Survival Procedures (CA209817) - All participants	• Added FACT-L collection during survival follow-up • Additional subsequent cancer therapy details added to subsequent therapy collection	• PRO collection added during survival follow-up visits to collect patient information • Additional information on data collection and timing provided for clarity

TABLE OF CONTENTS

1 SYNOPSIS

Clinical Protocol CA209817

Protocol Title: A Phase 3b/4 Safety Trial of Flat Dose Nivolumab in Combination with Ipilimumab in Participants with Non-Small Cell Lung Cancer

Study Phase:

Phase 3b/4

Rationale:

Given the promising efficacy data observed with combined programmed death-1 (PD-1) and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) blockade, and the expected logistical benefits of flat nivolumab dosing, a need was identified to characterize the safety of nivolumab flat dosing in combination with weight-based ipilimumab administration. The combination will initially be studied as first-line (Cohort A) or second-line (Cohort B) therapy in Stage IV or recurrent non-small cell lung cancer (NSCLC), administered as nivolumab 240 mg every (q) 2 weeks plus ipilimumab 1 mg/kg q6 weeks. Additionally, Cohort C will assess the combination in first line NSCLC participants whose tumors harbor a high mutation burden.

An optional exploratory analyses and data generation will be conducted in separate special population (Cohort A1) participants with nivolumab flat dosing in combination with weight-based ipilimumab administration at participating sites. Typically, ECOG PS 2, renal and hepatic impaired patients, asymptomatic brain metastases, and HIV patients are excluded from NSCLC trials. Limited data is available in these subpopulations. This study will allow for additional safety data with nivolumab plus ipilimumab in these special populations at participating sites.

Study Population:

Participants with metastatic or recurrent NSCLC in Cohorts A, B, C, and optional A1 cohort.

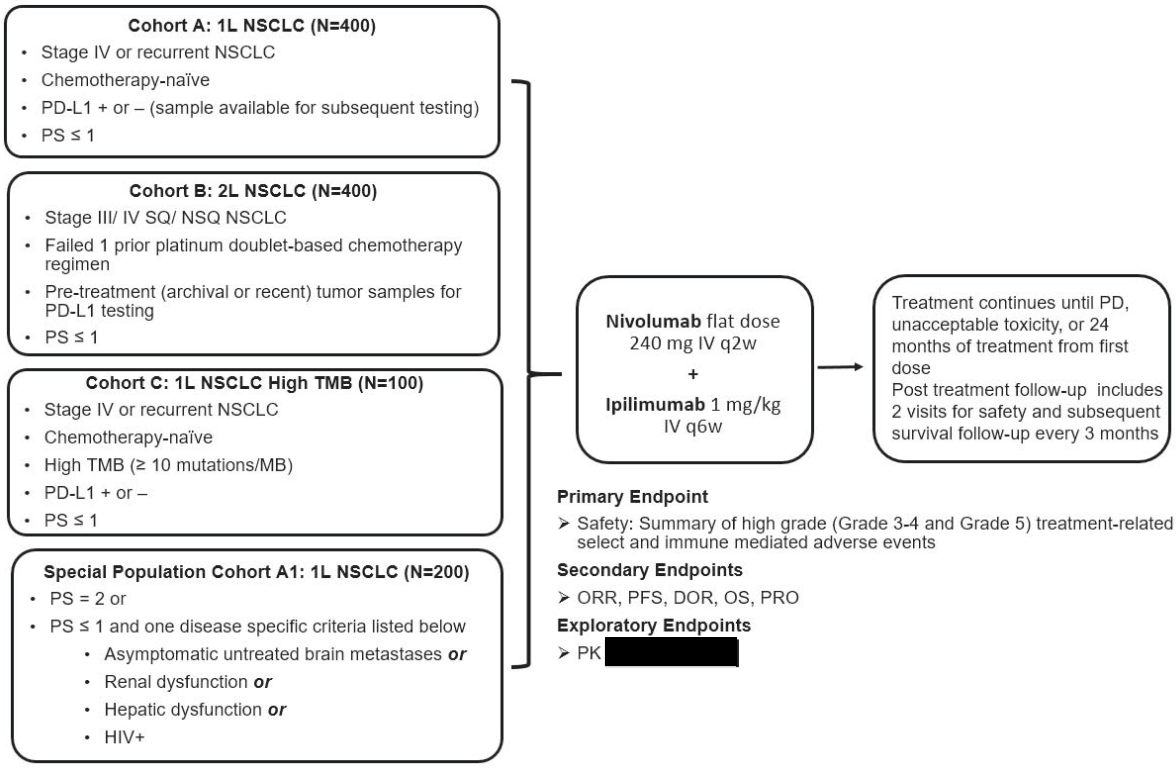
Objectives and Endpoints:

Objectives	Endpoints
Primary • To characterize the safety of nivolumab administered as a flat dose in combination with weight-based ipilimumab dosing in Cohorts A, B, and C.	• The primary objective of the study will be assessed by summarizing the number and percentage of participants who experience high grade (Grade 3-4 and Grade 5) treatment-related select and immune-mediated adverse events (imAEs) in Cohorts A, B, and C, analyzed separately. The select AEs of interest are the following: pneumonitis, interstitial nephritis, diarrhea/colitis, hepatitis, rash, endocrinopathies, and hypersensitivity/infusion reaction events.
Secondary To assess progression-free survival (PFS), overall survival (OS), duration of response (DOR) of nivolumab administered as a flat dose in combination with weight-based ipilimumab dosing in Cohorts A, B, and C.	• PFS defined as the time from first dosing date to the date of the first documented tumor progression, as determined by investigators (per Response Evaluation Criteria in Solid Tumors [RECIST] v1.1), or death due to any cause, whichever occurs first. • OS defined as the time from first dosing date to the date of death. • DOR defined as the time between the date of first confirmed response to the date of the first documented tumor progression (per RECIST 1.1), or death due to any cause, whichever occurs first
To assess the objective response rate (ORR) in Cohorts A, B, and C.	• ORR is defined as the number and percentage of participants with a best overall response (BOR) of confirmed complete response (CR) or partial response (PR). Best overall response (BOR) is defined as the best response designation, recorded

Objectives	Endpoints
	between the date of first dose and the date of the initial objectively documented tumor progression per RECIST v1.1 or the date of subsequent therapy, whichever occurs first.
To assess patient reported outcomes (PROs) in all treated participants	• Patient reported outcomes (PROs): assessment of changes in disease-related symptoms and function dimensions of Health Related Quality of Life (HRQoL) using Functional Assessment of Cancer Therapy-Lung (FACT-L)
Exploratory • To characterize the pharmacokinetics, immunogenicity, [redacted] of nivolumab administered as a flat dose in combination with weight-based ipilimumab dosing. • To assess safety in the NSCLC special population cohort (A1) • To estimate the efficacy of nivolumab administered as a flat dose in combination with weight-based ipilimumab dosing in the NSCLC special population cohort (A1). • To assess the feasibility of prospective TMB testing in Cohort C	• The pharmacokinetic (PK) objective will be measured from serum concentration. Samples will be collected to characterize the PK of nivolumab in combination with ipilimumab and to explore exposure-safety and exposure-efficacy relationships. • Exploratory immunogenicity [redacted] analyses will be performed. • Treatment-related select AEs, SAEs, and immune-mediated AEs in the NSCLC special population cohort. • Progression-free survival (PFS) • Objective Response Rate (ORR) • Overall survival (OS) • Duration of Response (DOR) • Participant reported outcomes (PROs) • Screen failure rate (Cohort C)

Overall Design:

- Four cohort, open-label study of first-line (Cohort A), second-line (Cohort B), first-line special population (Cohort A1), and first-line high TMB (Cohort C) receiving nivolumab and ipilimumab treatment
- Participants will receive treatment with nivolumab 240 mg as a 30 minute infusion every 2 weeks and ipilimumab 1 mg/kg as a 30 minute infusion every 6 weeks, starting on Day 1, until progression, unacceptable toxicity, withdrawal of consent, 24 months of treatment from the first dose, or the study ends, whichever occurs first.
- Follow up data will be collected for up to 5 years. At the conclusion of the study, participants who are determined to be benefitting from study treatment may be eligible to continue receiving study drug as described in Section 7.8.



Number of Participants:

Approximately 500 participants are expected to be enrolled in each of the primary cohorts: Cohort A (first-line NSCLC) and Cohort B (second-line NSCLC) to achieve approximately 400 treated participants in each cohort.

An additional, special population of NSCLC patients, Cohort A1, will include approximately 200 treated participants. Site participation in Cohort A1 is optional.

For Cohort C (first-line NSCLC), an estimated 300 participants will be screened to achieve approximately 100 participants with high TMB. Participation in Cohort C will be limited to US sites due to the TMB processing being conducted at a single US-based facility.

Treatment Arms and Duration:

Study treatment:

Study Drug for CA209817		
Medication	**Potency**	**Investigational Product (IP) /Non-IP**
Nivolumab	10 mg/ml	IP
Ipilimumab	5 mg/ml	IP

Participants in Cohort A (first-line NSCLC), Cohort B (second-line NSCLC), Cohort C (first-line NSCLC with high TMB), and special population cohort (A1) will receive treatment with nivolumab 240 mg as a 30 minute infusion every 2 weeks and ipilimumab 1 mg/kg as a 30 minute infusion every 6 weeks, starting on Day 1, until progression, unacceptable toxicity, withdrawal of consent, 24 months of treatment from first dose, or the study ends, whichever occurs first.

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (CA209817)

Procedure	Screening Visit (≤ 42 days)	Notes
Eligibility Assessments		
Informed Consent	X	Informed Consent may be obtained within 42 days prior to first dose and initial IVRS call prior to any study specific procedure
Inclusion/Exclusion Criteria	X	Section 6 All inclusion/exclusion criteria should be assessed prior to first dose
Medical History	X	
Safety Assessments		
Physical Measurements/Physical Examination	X	Include Height and Weight. Within 42 days prior to first dose
Vital Signs	X	Including BP, HR, & temperature. Obtain at the screening visit and within 72 hours prior to first dose.
Assessment of Baseline Signs and Symptoms	X	Assess within 14 days prior to first dose.
Serious Adverse Events (SAEs)		Collected after signing the informed consent
Concomitant Medication Collection	X	Collect within 14 days prior to first dose through the study treatment period.
Pregnancy Test (WOCBP only)	X	Section 6.1 Within 24 hours prior to Day 1/Negative pregnancy test required at Screening. (An extension up to 72 hours prior to start of study drug may be permissible in situations where results cannot be obtained within the standard 24 hour window).
FSH Level	X	Post-menopausal females under age 55 years must have serum FSH level > 40 mIU to begin study treatment (Appendix 4).

Table 2-1: Screening Procedural Outline (CA209817)

Procedure	Screening Visit (≤ 42 days)	Notes
Laboratory Tests	X	Section 9.4.2 CBC w/differential, Chemistry panel within 14 days prior to first dose. Hep B/C (HBV sAg, HCV antibody or HCV RNA), within 28 days prior to first dose. HIV test for all participants in Germany.
ECG (12-lead)	X	Section 9.4.1 Obtained only for participants who have met all eligibility criteria
Efficacy Assessments		
Radiographic Tumor Assessments(chest, abdomen, pelvis, brain)	X	Section 9.1.1, Appendix 6 Performed within 28 days prior to first dose. CT with IV contrast of Chest, Abdomen, Pelvis and all known or suspected sites of disease should be imaged at the screening visit. MRI with gadolinium may be obtained if CT iodinated contrast is contraindicated. MRI of brain without and with gadolinium is required for all participants during screening to rule out brain metastases. CT of the brain (without and with contrast) can be performed if MRI is contraindicated. See Section 9.1 for further details
Biomarker Assessments		
Archived Tumor Tissue or Recent Tumor Biopsy	X	Section 9.8.1 **For Cohorts A, A1, and B:** Fresh or archival sample, obtained within 12 months prior to enrollment. If archived slides are to be submitted, they must not have been cut > 6 months prior to submission, as sample may have degraded. One formalin-fixed paraffin embedded tumor tissue block or a minimum of 10 to 15 unstained tumor tissue sections are acceptable. **For Cohort C:** • Fresh or archival sample, obtained within 3 months prior to enrollment. • Submission of 10 unstained tumor tissue sections for TMB testing by Foundation Medicine unless TMB results from Foundation Medicine is already available (Note: participants may not enter treatment phase unless known results are TMB high) Submission of 5 additional slides for PD-L1 testing if results are not already available from another BMS study, or a commercially available complementary diagnostic using an acceptable antibody (ie, 28-8, 22-C3, SP263). PD-L1 results obtained using antibody SP142 are not acceptable.

Table 2-1: Screening Procedural Outline (CA209817)

Procedure	Screening Visit (≤ 42 days)	Notes
[redacted]		
EGFR Mutation and ALK Translocation Statuses	X	To be performed for all non-squamous participants (unless harboring known KRAS mutation). EGFR and ALK tests may be performed locally or at a central laboratory. May be performed outside the Screening period window, eg, > 42 days prior to first dose.
IVRS /Clinical Drug Supplies		
IRT	X	Section 7.2 For participant number assignment at the time informed consent is obtained

Table 2-2: Treatment Phase Assessments (CA209817)

Procedure[a]	Cycle 1 Day 1	Each Subsequent Cycle Day 1 (± 5 Days)	Day 15 and 29 of each Cycle (± 5 Days)	Notes For purposes of this table, a cycle refers to 6 weeks of treatment.
Safety Assessments				
Physical Measurements	X	X		Include Height and Weight.
Targeted Physical Exam		X		
ECOG Performance Status	X	X		See Appendix 5
Vital Signs	X	X		See Section 9.4. Vital signs should be assessed at each on-study visit prior to dosing.
Adverse Event Assessments	Continuously during the study			Section 9.2. SAEs should be approved within 5 days from entry.
Review of Concomitant Medications	X	X		
Laboratory Tests	X	X		Section 9.4.2 Within 72 hrs prior to dosing. **Note:** C1D1 labs do not need to be repeated if they were performed within 14 days of dosing. Creatinine clearance will be measured every 6 weeks for participants with renal impairment.
Pregnancy Test (WOCBP only)	X	X		To be evaluated at least every 6 weeks.

Table 2-2: Treatment Phase Assessments (CA209817)

Procedure[a]	Cycle 1 Day 1	Each Subsequent Cycle Day 1 (± 5 Days)	Day 15 and 29 of each Cycle (± 5 Days)	Notes For purposes of this table, a cycle refers to 6 weeks of treatment.
Efficacy Assessments				
Radiographic Tumor Assessment (CT chest and known sites of disease. Repeat CT/MRI of abdomen with or without pelvis is required for participants with metastases in those areas at baseline, or if clinically indicated.)	Section 9.1 Tumor assessments should occur every 6 weeks (± 7 days) up to Week 48, then every 12 weeks until documented radiographic disease progression. Participants with a history of known brain metastasis must have surveillance MRI study per standard of care (approximately every 12 weeks), or sooner if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1 for further details.			
Patient Reported Outcomes				
FACT-L	X	X		The FACT-L will be administered on Day 1 for the first 3 Cycles (Cycle 1 Day 1, W6 and W12). Thereafter it will be administered every 2 Cycles (Weeks 24, 36, 48, etc). On the day of study visits that include FACT-L assessment, the assessment will be performed PRIOR to any study procedures and treatment. Section 9.10
Pharmacokinetic (PK) and Immunogenicity Assessments				
PK Samples	Throughout the study			Section 9.5.1
Immunogenicity Samples	Throughout the study			Section 9.5.1
[redacted]				
Clinical Drug Supplies				
IRT Vial Assignment	X	X	X	Section 7.2. Within 3 business days prior to dosing
Nivolumab 240 mg[b,c]	X	X	X	Section 7.1[c]
Ipilimumab 1 mg/kg[c]	X	X		Section 7.1[c]

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

[b] Continues until disease progression, discontinuation due to unacceptable toxicity, 24 months of treatment, withdrawal of consent, or study closure.

[c] Dosing window: nivolumab ± 5 days unless dose frequency is less than 12 days and ipilimumab ± 5 days unless dose frequency is less than 37 days)

Table 2-3: Follow-up and Survival Procedures (CA209817) - All participants

Procedure	Follow-Up Visits 1 & 2[a]	Survival Follow-up Visits[b]	Notes
Safety Assessments			
Targeted Physical Examination	X		Section 9.4.1. To assess for potential late emergent study drug related issues.
Vital Signs	X		Section 9.4
Adverse Event Assessment	X		Section 9.2. SAEs should be approved within 5 days from entry. Beyond 100 days from the last dose of study drug, participants will be followed for ongoing drug-related adverse events until resolved, return to baseline or deemed irreversible, or until lost to follow-up, withdrawal of study consent, or start of subsequent therapy.
Review of Concomitant Medications	X		
Laboratory Tests	X		Section 9.4.2. Required at Visit 1. Repeat at Visit 2 only if study drug related toxicity persists.
Pregnancy Test (WOCBP only)	X		Section 9.2.5
Patient Reported Outcomes			
FACT-L	X	X	For participants who have discontinued study therapy, but continue to be followed for radiographic progression per Section 9.1.1, the FACT-L must be collected at each visit. On the day of study visits that include FACT-L assessment, the assessment will be performed PRIOR to any study procedures and treatment. FACT-L assessments may be administered in office or over the telephone. Section 9.10

Table 2-3: Follow-up and Survival Procedures (CA209817) - All participants

Procedure	Follow-Up Visits 1 & 2[a]	Survival Follow-up Visits[b]	Notes
Efficacy Assessments			
Radiographic Tumor Assessment (CT chest and known sites of disease. Repeat CT/MRI of abdomen with or without pelvis is required for participants with metastases in those areas at baseline, or if clinically indicated.)	X	X*	Section 9.1.1. For participants who discontinue study treatment for reasons other than progressive disease, follow up scans should be performed every 6 weeks (± 1 wk) up to Week 48, then every 12 weeks until progressive disease, initiation of subsequent systemic therapy, lost to follow-up, or withdrawal of consent. *Radiographic assessments for participants who have not experienced progressive disease ***must*** be obtained every 6 weeks (± 7 days), and ***not*** delayed until follow-up visits 1 & 2.
Collection of Survival Status and Subsequent Therapy Information	X	X	Collect **every 3 months** in Survival Visits until death, lost to follow-up, or withdrawal of study consent. May be performed by phone contact or office visit. Additional subsequent cancer therapy details such as regimen, setting of the regimen, line of therapy, start date and end date of each regimen, best response to the regimen and date of progression after second line therapy will be collected.

[a] Follow-Up Visit 1 to occur 35 days from the last dose (± 7 days) or coinciding with the date of discontinuation of study drug (± 7 days) if the date of discontinuation is greater than 42 days from the last dose. Follow-Up Visit 2 to occur 80 days from Follow-Up Visit 1 (± 7 days) . Patients should be monitored continuously (at least up to 100 days after the last dose) as an adverse reaction with nivolumab or nivolumab in combination with ipilimumab may occur at any time during or after discontinuation of therapy.

[b] Survival Follow-Up Visits to occur approximately every 3 months (± 14 days) from Follow-Up Visit 2.. Survival visit may be conducted in person or by telephone. BMS may request that survival data be collected on all treated participants outside of the 3 month specified window. At the time of this request, each participant will be contacted to determine their survival status unless the subject has withdrawn consent for all contact.

3 INTRODUCTION

Nivolumab Monotherapy

Nivolumab is now approved in the United States (US) and European Union (EU) to treat metastatic non-small cell lung cancer (NSCLC) in patients with progression on or after platinum-based chemotherapy.[1]

The approval in squamous NSCLC was based on the results of CA209017, a randomized phase 3 trial of nivolumab versus docetaxel. In this study, nivolumab demonstrated superior overall survival (OS) compared with docetaxel (median OS: 9.2 vs 6.0 months), with a clinically meaningful and statistically significant improvement observed (hazard ratio [HR] = 0.59; P = 0.0002). Improvement in survival was observed for nivolumab regardless of programmed death-ligand 1 (PD-L1) expression, though there was a trend for better efficacy for those with PD-L1 expressing tumors.[2] The objective response rate (ORR) was also significantly higher in the nivolumab group compared with the docetaxel group: 20.0% vs 8.8% (P = 0.0083).

The approval in non-squamous NSCLC was also based on a second Phase 3 study, CA209057, which met its primary endpoint of superior overall survival of nivolumab vs docetaxel in participants with previously treated non-squamous NSCLC at a preplanned interim analysis.[3] Participants in the nivolumab group had a 27% reduction in risk of death (HR = 0.73; P = 0.0015). Interaction p-values, reported for PD-L1 expression subgroups by each of the predefined expression levels, suggested a clinically important signal of a predictive association. Nivolumab also significantly improved ORR vs docetaxel (P = 0.0246), with ORR as high as 36% in participants with PD-L1 expressing tumors. OS approximately doubled with nivolumab vs docetaxel across the PD-L1 expression continuum. In contrast, no difference in OS was seen between nivolumab and docetaxel when PD-L1 was not expressed in the tumor.

Updated efficacy data for CA209017 and CA209057 is available with a minimum survival follow-up of 24.2 months in each study.[4,5] Nivolumab continued to demonstrate superior OS compared with docetaxel in both studies, with a clinically meaningful improvement observed; in CA209017, the HR was 0.62 (95% CI: 0.47, 0.80) and in CA209057, the HR was 0.74 (95% CI: 0.61, 0.88). In both studies the updated analysis for investigator-assessed confirmed ORR (and also the median duration of response [DOR] in CA209057) was unchanged from what was reported in the final clinical study report [CSR]. In the CA209017 final CSR, the median DOR for nivolumab was not reached; in the updated analysis, the median DOR was 25.20 months for nivolumab and 8.41 months for docetaxel.

In general, nivolumab has been well tolerated to date, with a favorable safety profile consistent with anticipated toxicities based on an immunostimulatory mechanism of action.[6]

Nivolumab in Combination with Ipilimumab

Preclinical data indicate that the combination of programmed death-1 (PD-1) and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) receptor blockade may improve antitumor activity. In vitro combinations of nivolumab plus ipilimumab increase interferon (IFN)-γ production 2- to

7-fold over either agent alone in a mixed lymphocyte reaction. Increased antitumor activity of the combination was also observed in 3 of 5 syngeneic murine cancer models. In a murine melanoma vaccine model, blockade with either CTLA-4 or PD-1 antibodies increased the proportion of CTLA-4 and PD-1-expressing CD4/CD8 tumor infiltrating T effector cells, and dual blockade increased tumor infiltration of T effector cells and decreased intratumoral T regulatory cells, as compared to either agent alone.[7]

Nivolumab and ipilimumab have been shown to have complementary activity in metastatic melanoma. CTLA-4 and PD-1 inhibit antitumor immunity through complementary and non-redundant mechanisms.[8]

High ORRs (including complete responses), a prolonged DOR, and a favorable OS rate of 79% at 2 years were observed in a Phase 1 dose-escalation study, CA209004, involving participants with advanced melanoma who received the combination regimen of nivolumab and ipilimumab.[9,10] Based on this, 2 large studies examining the combination of nivolumab and ipilimumab were performed (CA209067 and CA209069) and showed that the combination of nivolumab and ipilimumab has a favorable ORR. In CA209067, nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg demonstrated an ORR of 58%, numerically higher than either as single agents. In CA209069, the same combination doses achieved an ORR of 61%, significantly greater than that of ipilimumab alone (Table 3-1).

Table 3-1: Best Objective Response Rate of Nivolumab in Combination with Ipilimumab and as a Single Agent

	Nivo 3 mg/kg +Ipi 1 mg/kg	Nivo 1 mg/kg + Ipi 3 mg/kg	Nivo 3 mg/kg	Ipi 3 mg/kg
CA209004[9]	40%	50%	NA	NA
CA209067[11]	NA	58%	44%	19%
CA209069[12]	NA	61%	NA	11%

NA = Not Applicable

In a Phase 1 study in participants with previously untreated, advanced NSCLC (CA209012), the combination of nivolumab plus ipilimumab was evaluated at several different doses and schedules. While the schedule evaluated in melanoma was not found to be tolerable in NSCLC, the study identified alternative schedules with an acceptable tolerability profile and encouraging activity, with confirmed ORRs of up to 57% in PD-L1+ participants.[13] See Section 3.2.4 for more information. A Phase 3 study (CA209227) evaluating nivolumab monotherapy, nivolumab in combination with ipilimumab, and nivolumab in combination with chemotherapy, versus chemotherapy in first-line NSCLC is currently ongoing.

Incorporating a flat 240 mg dose of nivolumab into the combination regimen is expected to simplify treatment with nivolumab without impacting the overall safety profile of the combination. Detailed rationale for the use of a flat 240 mg dose of nivolumab is provided in Section 5.5.2.

Tumor Mutation Testing

Tumor mutation burden (TMB) refers to the total number of nonsynonymous somatic mutations that exist within a tumor's genome. A subset of these mutations, termed neo-antigens, may result in an expressed protein that is not recognized by the host's immune system as self, and therefore has the potential to be immunogenic, leading to an anti-tumor immune-mediated response. Tumors with a high mutation burden may have a higher rate of neo-antigens which, in principle, would be expected to be more immunogenic than tumors with comparatively low mutation burden.[14] Additional information is found in Section 5.5.5.

3.1 Study Rationale

Given the promising efficacy data observed with combined PD-1 and CTLA-4 blockade, and the expected logistical benefits of flat nivolumab dosing, a need was identified to characterize the safety of nivolumab flat dosing in combination with weight-based ipilimumab administration. The combination (nivolumab 240 mg q2 weeks plus ipilimumab 1 mg/kg q6 weeks) will be studied as first-line (Cohorts A, A1, and C) and second-line (Cohort B) treatment for Stage IV or recurrent NSCLC.

In CA209012, both the q6 week and q12 week cohorts were associated with improved and manageable tolerability compared to the cohorts with more frequent ipilimumab dosing (q3 weeks). Both cohorts also had encouraging efficacy with enhanced benefit observed in participants with PD-L1 expression, with the q6 week cohort having numerically higher median progression-free survival (PFS) compared to the q12 week cohort. With both schedules showing a similar safety and efficacy profile, and considering the imbalances in cohorts favoring the q12 week cohort, the q6 week schedule was chosen to avoid any potential loss of efficacy with less frequent dosing with longer follow-up.

3.1.1 Research Hypothesis

There is no formal statistical hypothesis. Analyses to characterize select and immune-related adverse events (imAEs) and efficacy in terms of objective response rate will be descriptive.

3.2 Background

3.2.1 Non-Small Cell Lung Cancer (NSCLC) Background

Lung cancer is the most common cancer worldwide, with 1.8 million new cases diagnosed yearly, and an estimated 1.6 million deaths worldwide.[15] NSCLC represents approximately 85% of all lung cancers and includes squamous cell carcinoma, adenocarcinoma, and large cell carcinoma, but in the broadest sense, may include any epithelial tumor that lacks a small-cell component. Non-squamous NSCLC accounts for approximately 75% to 85% of all NSCLC, and encompasses a variety of histological subtypes other than squamous, including adenocarcinoma, large cell carcinoma, and less common subtypes.[16,17,18,19]

First-Line Treatments for NSCLC

Metastatic or recurrent NSCLC remains an area of high unmet medical need as patients have a poor prognosis (5-year survival rate of ~ 1% for stage IV disease).[20] For the last several decades, chemotherapy doublets (mostly platinum-based) have been the recommended standard of care for initial treatment of metastatic or recurrent (ie, advanced) NSCLC. This recommendation is based on prolongation of OS relative to best supportive care (BSC)[21,22,23,24,25] or single agent chemotherapy.[26] Efficacy with first-line standard-of-care platinum-based chemotherapy regimens is modest (median OS: 10-13 months; median PFS: 5-6 months), and the vast majority of subjects experience disease progression with the first year of treatment, with only 10%-20% of subjects progression free at 18 months, and less than one-fourth to one-fifth of patients are still alive at 2 years.[27] More recently, tyrosine kinase inhibitors have been shown to be the optimal first-line therapy for patients with NSCLC tumors harboring known driver mutations (epidermal growth factor receptor [EGFR], anaplastic lymphoma kinase [ALK], and proto-oncogene tyrosine-protein kinase 1 [ROS-1]), but acquired resistance to these agents limits their long-term efficacy. First-line therapies that provide durable clinical benefit are needed for this high-risk population of patients with metastatic or recurrent NSCLC.

Currently, first-line treatment of NSCLC with immunotherapy agents is showing promise. Recently published initial data from the Keynote-024 study show that first-line treatment with pembrolizumab (a PD-L1 inhibitor) in participants with at least 50% PD-LI expression, produced an ORR of 44.8% compared with 27.8% for doublet chemotherapy and this resulted in a significant OS advantage for pembrolizumab (median OS was not reached in either group, HR = 0.60, 95% CI 0.41, 0.89, P = 0.005).[28]

Second-Line Treatments for NSCLC

Nivolumab monotherapy and other PD-L1 inhibitors have become the standard of care for second-line treatment of NSCLC. As mentioned in Section 3, nivolumab has been approved as therapy for metastatic NSCLC in patients with progression on or after platinum-based chemotherapy. This approval is based on superior OS compared with docetaxel in 2 phase 3 studies (CA209017 and CA209057). Bristol-Myers Squibb (BMS) is currently investigating the combination of nivolumab and ipilimumab as second-line treatment of NSCLC in several ongoing studies. Despite the recent advances with immuno-oncology drugs (improvement in OS), many patients do not derive long-term benefit with from monotherapy with checkpoint inhibitors.

Therapeutic options for mutation wild-type non-squamous NSCLC are particularly limited after failure of front-line chemotherapy. Overall, this group of patients only has an OS of about 8 months after progression from platinum agents. Once resistance to tyrosine kinase inhibitors (TKIs) occurs, the patients who have EGFR mutations or ALK translocations will have a rapid disease progression.

Unlike patients with non-squamous histology NSCLC, patients with squamous cell NSCLC have generally not benefitted from (and in fact may be negatively impacted by) several new agents, including pemetrexed and bevacizumab.[29,30] Therapeutic options for squamous cell NSCLC have been particularly limited after failure of front-line chemotherapy.

3.2.2 Nivolumab Mechanism of Action

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses.[31,32,33] Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor.[34] Collectively, these signals govern the balance between T-cell activation and tolerance.

PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA 4, ICOS, and BTLA.1 PD-1 signaling has been shown to inhibit CD-28-mediated upregulation of interleukin (IL)-2, IL-10, IL-13, IFN-γ and Bcl-xL. PD-1 expression also been noted to inhibit T cell activation, and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes.[35] These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

In vitro, nivolumab (BMS-936558) binds to PD-1 with high affinity (median effective concentration [EC50] 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (50% inhibitory concentration [IC50] ≤ 1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4 and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction (MLR). Using a cytomegalovirus (CMV) restimulation assay with human peripheral blood mononuclear cells (PBMC), the effect of nivolumab on antigen specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV specific memory T cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and results in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[36]

3.2.3 Ipilimumab Mechanism of Action

CTLA-4, an activation-induced T-cell surface molecule, is a member of the CD28:B7 immunoglobulin superfamily that competes with CD28 for B7. CTLA-4 mediated signals are inhibitory and turn off T cell-dependent immune responses.[37] Ipilimumab is a fully human monoclonal immunoglobulin (Ig)G1κ that binds to the CTLA-4 antigen expressed on a subset of T cells from human and nonhuman primates. The proposed mechanism of action for ipilimumab is interference of the interaction of CTLA-4 with B7 molecules on antigen presenting cells (APCs), with subsequent blockade of the inhibitory modulation of T-cell activation promoted by the CTLA 4/B7 interaction.

3.2.4 Nivolumab Combined with Ipilimumab

CA209012 was a multi-cohort Phase 1 trial evaluating the safety and tolerability of nivolumab as either a monotherapy or in combination with other agents including ipilimumab, at different doses and schedules in participants with chemotherapy-naïve advanced NSCLC. The primary endpoint of the study was safety with secondary endpoints of ORR and 24-week PFS. Exploratory endpoints included OS and efficacy by PD-L1 expression. In this study, participants were tested for PD-L1 expression and 68% of participants in the q12 week cohort and 77% of participants in the q6 week cohort expressed PD-L1.

The efficacy and safety results of the 3 dosing schedules in CA209012 (nivolumab 3 mg/kg q2 weeks plus ipilimumab 1 mg/kg q12 weeks, nivolumab 3 mg/kg q2 weeks plus ipilimumab 1 mg/kg q6 weeks, and nivolumab 3 mg/kg q2 weeks as monotherapy) are described in Table 3.2.4-1 and Table 3.2.4-3.[13] Updated efficacy results for the 2 combination cohorts are provided in Table 3.2.4-2.

Table 3.2.4-1: CA209012 Efficacy Results

	Nivo 3 Q2W + Ipi 1 Q12W (n = 38)	Nivo 3 Q2W + Ipi 1 Q6W (n = 39)	Nivo 3 Q2W (n = 52)
Confirmed ORR, % (95% CI)	47 (31, 64)	39 (23, 55)	23 (13, 37)
Median duration of response, mo (95% CI)	NR (11.3, NR)	NR (8.4, NR)	NR (5.7, NR)
Median length of follow-up, mo (range)	12.9 (0.9–18.0)	11.8 (1.1–18.2)	14.3 (0.2–30.1)

Table 3.2.4-2: CA209012 Updated Efficacy Results

	Nivo 3 Q2W + Ipi 1 Q12W (n = 38)	Nivo 3 Q2W + Ipi 1 Q6W (n = 39)
Confirmed ORR, % (95% CI)	47 (31, 64)	39 (23, 55)
1 year OS Rate, %	83.3	69.0
Minimum length of follow-up, mo	16	16

The rate of treatment-related AEs in the q12 weeks (82%) and q6 week (72%) cohorts were comparable to monotherapy (72%) (Table 3.2.4-3). In the study, Grade 3/4 AEs were 37%, 33%, and 19% for the q12 weeks, q6 weeks and nivolumab monotherapy cohorts, respectively. Treatment-related Grade 3-4 AEs lead to discontinuation in 5% and 8% of participants in the q12 week and q6 week cohorts, respectively and were similar to nivolumab monotherapy. There were no treatment-related deaths. The treatment-related select AEs in participants administered the optimized dosing scheduled (3 mg/kg of nivolumab q2 weeks plus 1 mg/kg of ipilimumab q6 weeks) were skin related (36%), gastrointestinal (23%), endocrine (20%), and pulmonary (5%) and there were ≤ 5% treatment related grade 3/4 AEs per category.

Table 3.2.4-3: CA209012 Safety Results

	Nivo 3 Q2W + Ipi 1 Q12W (n = 38)		**Nivo 3 Q2W + Ipi 1 Q6W (n = 39)**		**Nivo 3 Q2W (n = 52)**	
Reason for Discontinuation						
Death, n (%)	11 (28.9)		15(38.5)		33(63.5)	
Disease Progression, n (%)	9 (23.7)		13(33.3)		31(59.6)	
Study Drug Toxicity, n (%)	0		0		0	
Unknown, n (%)	1(2.6)		0		1(1.9)	
Other reason, n (%)	1(2.6)		2(5.1)		1(1.9)	
	Any Grade	**Grade 3/4**	**Any Grade**	**Grade 3/4**	**Any Grade**	**Grade 3/4**
Treatment-related AEs, %	82	37	72	33	72	19
Treatment-related AEs leading to discontinuation, %	11	5	13	8	10	10
All SAEs, %	60.5		62		41	
Treatment-related select AEs, %	**Grade 1/2**	**Grade 3/4**	**Grade 1/2**	**Grade 3/4**	**Grade 1/2**	**Grade 3/4**
Skin related	37		3	5	21	4
Gastrointestinal	18		5	5	10	2
Endocrine	8		3	5	14	0
Pulmonary	5		5	3	4	2

3.3 Benefit/Risk Assessment

Patients with metastatic or recurrent NSCLC represent an important unmet medical need. The clinical activity of nivolumab plus ipilimumab observed to date in NSCLC suggests the potential for improved clinical outcomes in first-line and second-line settings.

CA209012 showed confirmed response rates of 39% to 47% with nivolumab 3 mg/kg q2 weeks and ipilimumab 1 mg/kg q6 weeks or q12 weeks. Activity was observed in both PD-L1

expressing and non-expressing NSCLC, however, higher response rates were observed in patients whose tumors express PD-L1 (≥ 1%, confirmed response rate of 57%). Updated efficacy results from CA209012, show that the confirmed response rates were unchanged, but the 1-year OS rates were 83.3% and 69.0% with nivolumab 3 mg/kg q2 weeks plus ipilimumab 1 mg/kg q12 weeks and nivolumab 3 mg/kg q2 weeks plus ipilimumab 1 mg/kg q6 weeks, respectively.

The safety profile of nivolumab and nivolumab plus ipilimumab is characterized by immune-related toxicities, such as diarrhea, rash, pneumonitis, liver toxicity, and endocrinopathies. The frequencies and intensities of these events in the combination are variable and depend on the specific doses and schedule used. In the dosing schedules selected, these events were mostly low grade, and manageable with the use of corticosteroids. Nivolumab and ipilimumab combination therapy has shown improved efficacy over either agent alone in melanoma. The flat dose of nivolumab 240 mg is not anticipated to change the overall risk/benefit ratio for the combination.

To assure an ongoing favorable risk/benefit assessment for participants enrolled into CA209817, high-grade, treatment-related AEs will be closely monitored throughout the conduct of the trial. The Medical Monitor will be responsible for reviewing, on a systematic and continuous basis, the safety of participants on this study. This includes a review of serious AEs (SAEs) and non-serious AEs.

More detailed information about the known and expected benefits and risks and reasonably anticipated AEs of nivolumab and ipilimumab may be found in the Investigator Brochure.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To characterize the safety of nivolumab administered as a flat dose in combination with weight-based ipilimumab dosing in Cohorts A, B, and C.	• The primary objective of the study will be assessed by summarizing the number and percentage of participants who experience high grade (Grade 3-4 and Grade 5) treatment-related select and immune-mediated adverse events (imAEs) in Cohorts A, B, and C, analyzed separately. The select AEs of interest are the following: pneumonitis, interstitial nephritis, diarrhea/colitis, hepatitis, rash, endocrinopathies, and hypersensitivity/infusion reaction events.
Secondary	
• To assess progression-free survival (PFS), overall survival (OS), duration of response (DOR) of nivolumab administered as a flat dose in combination with weight-based ipilimumab dosing in Cohorts A, B, and C.	• PFS defined as the time from first dosing date to the date of the first documented tumor progression, as determined by investigators (per Response Evaluation Criteria in Solid Tumors [RECIST] v1.1), or death due to any cause, whichever occurs first. • OS defined as the time from first dosing date to the date of death.

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
	• DOR defined as the time between the date of first confirmed response to the date of the first documented tumor progression (per RECIST 1.1), or death due to any cause, whichever occurs first
• To assess the objective response rate (ORR) in Cohorts A, B, and C.	• ORR is defined as the number and percentage of participants with a best overall response (BOR) of confirmed complete response (CR) or partial response (PR). Best overall response (BOR) is defined as the best response designation, recorded between the date of first dose and the date of the initial objectively documented tumor progression per RECIST v1.1 or the date of subsequent therapy, whichever occurs first.
• To assess patient reported outcomes (PROs) in all treated participants	• Patient reported outcomes (PROs): assessment of changes in disease-related symptoms and function dimensions of Health Related Quality of Life (HRQoL) using Functional Assessment of Cancer Therapy-Lung (FACT-L)
Exploratory	
• To characterize the pharmacokinetics, immunogenicity, [redacted] of nivolumab administered as a flat dose in combination with weight-based ipilimumab dosing.	• The pharmacokinetic (PK) objective will be measured from serum concentration. Samples will be collected to characterize the PK of nivolumab in combination with ipilimumab and to explore exposure-safety and exposure-efficacy relationships. • Exploratory immunogenicity [redacted] analyses will be performed.
• To assess safety in the NSCLC special population cohort in optional Cohort A1	• Treatment-related select AEs, SAEs, and immune-mediated AEs in the NSCLC special population cohort.
• To estimate the efficacy of nivolumab administered as a flat dose in combination with weight-based ipilimumab dosing in the NSCLC special population cohort in optional Cohort A1	• PFS, ORR, OS, DOR, PROs
• To assess the feasibility of prospective TMB testing in Cohort C	• Screen failure rate (Cohort C)

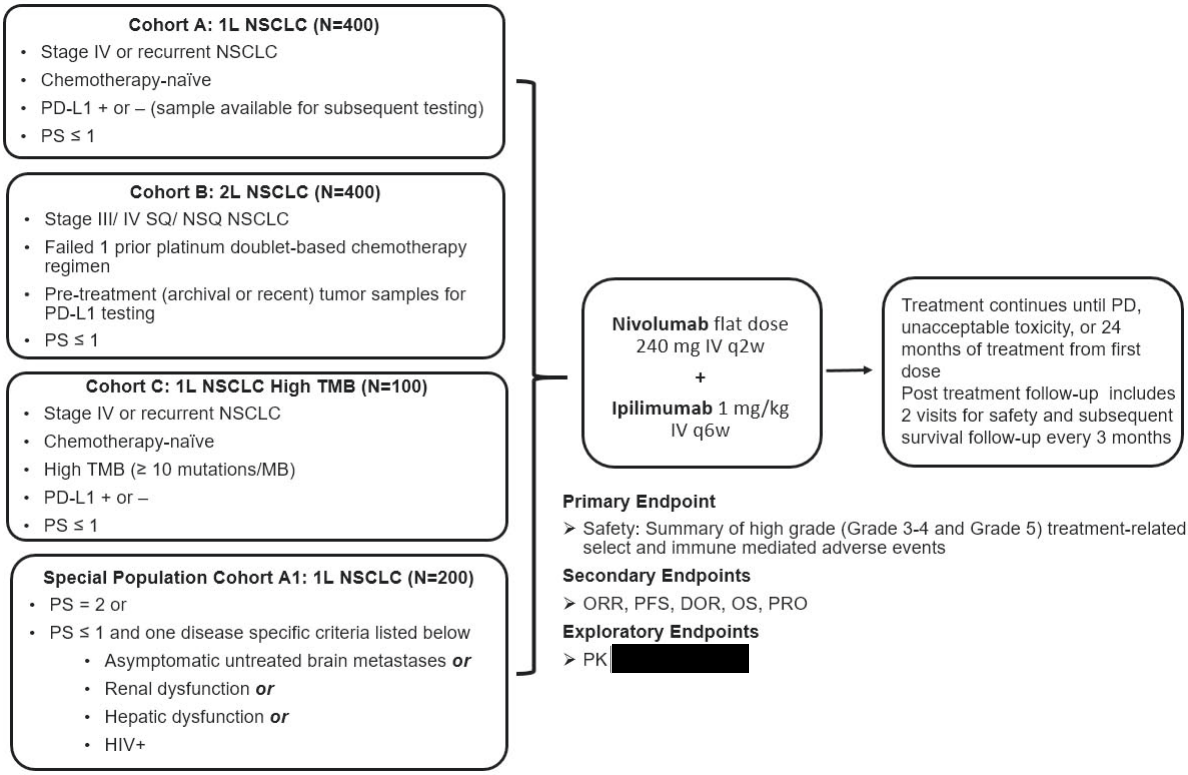
5 STUDY DESIGN

5.1 Overall Design

In this Phase 3b/4 open-label study of nivolumab in combination with ipilimumab in multiple tumor types, participants will receive flat dose nivolumab combined with weight-based ipilimumab treatment as described in Section 7.1. Cohort A will include participants with NSCLC receiving nivolumab in combination with ipilimumab as first-line treatment. Cohort B will include participants with NSCLC receiving nivolumab in combination with ipilimumab as second-line treatment. Cohort C will evaluate the safety of flat dose nivolumab with weight-

based ipilimumab as first-line treatment in patients with NSCLC whose tumor harbors a high mutation burden, as well as the clinical activity and the feasibility of prospective TMB testing in the setting of first-line NSCLC. An additional special population (Cohort A1) will include participants in special population subgroups and will include with one of the following criteria (as defined in Section 6.1.1): ECOG PS 2 or ECOG PS ≤1 with asymptomatic untreated brain metastases, renal dysfunction, hepatic dysfunction, or HIV. Follow up data will be collected for up to 5 years. Participants who are determined to be benefitting from study treatment after analysis of the primary endpoint is completed may be eligible to continue receiving study drug as described in Section 7.8. The study design schematic is presented in Figure 5.1-1.

Figure 5.1-1: CA209817 Study Design Schematic



Physical examinations, vital sign measurements, 12-lead electrocardiograms (ECG), and clinical laboratory evaluations will be performed at selected times throughout the dosing interval. Participants will be closely monitored for adverse events (AEs) throughout the study.

5.1.1 Dosing

Participants in all cohorts will receive nivolumab 240 mg q2 weeks in combination with ipilimumab 1 mg/kg q6 weeks until disease progression, unacceptable toxicity, 24 months treatment from first dose, or other stopping criteria as described in Section 8.

5.1.2 Data Monitoring Committee

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

A Data Monitoring Committee (DMC) will not be utilized for this study, with the following rationale:

1) This study is a 4-cohort, open-label study (Cohort A, Cohort A1, Cohort B, and Cohort C).
2) Data from the ongoing Phase 1 CA209012 study has demonstrated that the combination of nivolumab and ipilimumab at the schedule proposed for the current CA209817 study has a manageable safety profile that is consistent with prior experience with these agents.
3) The ongoing CA209227 Phase 3 study is utilizing the same treatment combination and schedule for 2 of the 6 cohorts in the trial, and is being conducted with DMC oversight. The DMC convened on 28-Jun-2016, reviewing available data on 378 treated participants (including > 100 participants treated with nivolumab + ipilimumab), and recommended that the study continue as planned.
4) Safety data will be closely monitored by BMS, with real time review and assessment of SAEs as they are received, and periodic review of all AE data for potential new safety signals.
5) Safety data for participants enrolled in the NSCLC special population cohort will be reviewed by the BMS Medical Monitor on a monthly basis until all participants have been enrolled in the cohort and have been followed for at least 3 months.

5.2 Number of Participants

5.2.1 All Cohorts (NSCLC)

Approximately 500 participants are expected to be enrolled in Cohort A (first-line NSCLC) and in Cohort B (second-line NSCLC) to achieve approximately 400 treated participants in each cohort.

An additional special population NSCLC cohort (Cohort A1) will include approximately 200 treated participants in the special population subgroup. These subgroups include participants with the following criteria (as defined in Section 6.1.1): ECOG PS 2 or ECOG PS ≤1 with asymptomatic untreated brain metastases, renal dysfunction, hepatic dysfunction, or HIV. Site participation in Cohort A1 is optional.

An estimated 300 participants will be screened to achieve approximately 100 TMB high treated participants in Cohort C (first-line NSCLC). Participation in Cohort C will be limited to US sites.

5.3 End of Study Definition

The start of the trial is defined as the first visit for the first participant screened. End of trial is defined as the last visit for the last participant.

5.4 Scientific Rationale for Study Design

The CA209817 study has been designed to demonstrate that flat dose nivolumab can be safely combined with weight-based ipilimumab dosing. With a sample size of 400 treated participants in the NSCLC Cohort A and 400 treated participants in the NSCLC Cohort B, the study will adequately characterize the safety profile of nivolumab 240 mg q2 weeks in combination with

ipilimumab 1 mg/kg q6 weeks in participants with metastatic or recurrent NSCLC receiving first-line or second-line treatment.

Cohort C will assess the safety of flat dose nivolumab and weight-based ipilimumab combination treatment in high TMB patients with NSCLC in the first line setting. Additionally, the clinical activity of the combination and TMB testing feasibility will be evaluated in the same 1L NSCLC cohort. Participants will have tissue screened prospectively for high TMB, defined as ≥ 10 mutations per million base pairs (MB). Analysis of internal data from ongoing immuno-oncology studies in the BMS lung program showed that a cut-off of 10 mutations/MB defined the highest efficacy when balanced against prevalence in the population of NSCLC patients treated with nivolumab (with or without ipilimumab). Participants in Cohorts A, A1, and B will have retrospective testing of TMB if sufficient tissue is available.

Exploratory analyses and data generation will be conducted in special population participants (Cohort A1) with nivolumab flat dosing in combination with weight-based ipilimumab administration at participating sites. Typically, ECOG PS 2, renal and/or hepatic impaired patients, asymptomatic brain metastases, and HIV patients are excluded from NSCLC trials. Limited data are available in these subpopulations. The safety of nivolumab monotherapy has been demonstrated in patients aged ≥ 70 years or with ECOG PS 2 in the CA209-153 trial, and in patients with asymptomatic untreated brain metastases in the CA209-012 study.[38] T

5.5 Justification for Dose

The dose and schedule of nivolumab and ipilimumab for use in all cohorts of the trial was selected based on the data observed in the CA209012 study.[13] The CA209012 study demonstrated activity of the combination of nivolumab 3 mg/kg q2 weeks plus ipilimumab 1 mg/kg q6 weeks in both PD-L1+ and PD-L1- tumors, coupled with a manageable safety profile.

While the CA209012 study implemented weight-based dosing of 3 mg/kg for nivolumab, a flat dose of 240 mg will be utilized in CA209817.

5.5.1 Rationale for Schedule

In CA209012, both the q6 week and q12 week cohorts were associated with improved and manageable tolerability compared to the cohorts with more frequent ipilimumab dosing (q3 weeks). Both cohorts also had encouraging efficacy in all participants and enhanced benefit in patients with PD-L1 expression, with q6 week cohort having numerically higher median PFS compared to the q12 week cohort. There were some imbalances observed between the q6 week and q12 week cohorts, as follows:

- There were more never smokers in Cohort Q (q6 week schedule) than Cohort P (q12 week schedule). Current and former smokers have been shown to respond better to immunotherapy.
- Participants in Cohort Q progressed, died or came off treatment more frequently in the first 3 months; however, this did not appear to be related to the schedule.

- Overall treatment related AEs leading to discontinuation as rates were 11% and 13% in the q12 week and q6 week cohort, respectively. While there were more AEs leading to discontinuation in the first 3 months in Cohort Q (n = 3) versus Cohort P (n = 1), 2 of the 3 patients who discontinued < 3 months on Cohort Q discontinued before receiving the 2nd dose of ipilimumab, and, therefore, these discontinuations are unlikely to be due to the more frequent dosing on the q6 week cohort.
- There were early clinical progressors and (unrelated) deaths in the q6 week cohort compared to the q12 week cohort (8% and 15%), more likely due to imbalances in baseline characteristics, rather than differences in treatment schedule.

With both schedules showing a similar safety and efficacy profile, and considering imbalances in treatment arms favoring the q12 week cohort, the q6 week schedule was chosen to avoid any potential loss of efficacy with less frequent dosing with longer follow up.

5.5.2 Rationale for Nivolumab 240 mg Dose

Nivolumab monotherapy has been extensively studied in the NSCLC patient population in studies CA209003, CA209063, CA209017, and CA209057, with body weight normalized dosing (mg/kg). Nivolumab pharmacokinetics (PK) and exposures of participants in these studies in NSCLC have been characterized by population pharmacokinetic (PPK) analysis of data collected from these studies, together with PK data from several Phase 1, 2, and 3 clinical studies of nivolumab monotherapy in solid tumors.

Nivolumab PK was determined to be linear, with dose proportional exposures over a dose range of 0.1 to 10 mg/kg. Nivolumab clearance and volume of distribution was found to increase with increasing body weight, but the increase was less than proportional, indicating that a mg/kg dose represents an over-adjustment for the effect of body weight on nivolumab PK.

Flat dosing offers several advantages over body weight normalized dosing, including reduced potential for dosing errors and shortened dosage preparation time. A flat dose of 240 mg every 2 weeks is expected to produce the equivalent average exposure to 3 mg/kg every 2 weeks at the median body weight of ~80 kg in nivolumab-treated participants.

A PPK model predicted overall nivolumab exposures across participants with a wide range of body weight (35-160 kg) for a 240 mg every 2 weeks flat dose to be similar to that from 3 mg/kg every 2 weeks. Although the flat dose is expected to lead to higher exposure in lighter patients, relative to the exposure in heavier patients given the relationship between nivolumab PK and body weight, the predicted median and 95th percentile of exposures from these regimens are maintained well below those in 10 mg/kg every 2 weeks, which was established as a safe and well-tolerated dose.

In addition, the relationship between nivolumab exposure produced by 3 mg/kg and efficacy has been found to be relatively flat. Taken together, the PK, safety, and efficacy data indicate that the safety and efficacy profile of 240 mg nivolumab will be similar to that of 3 mg/kg nivolumab.

5.5.3 Rationale for Two Year Duration of Treatment

The optimal duration of immunotherapy is an important question and continues to be investigated. Accumulating evidence from different clinical trials across different tumor types with nivolumab and ipilimumab indicate that most of the responses occur early, with a median time to response of 2 to 4 months including in patients with NSCLC. A recent analysis in a melanoma study suggests the majority of patients who discontinue nivolumab and/or ipilimumab for toxicity maintain disease control in the absence of further treatment.[39] Furthermore, a limited duration of ipilimumab (including patients receiving only 4 induction doses) resulted in the long term survival of patients with metastatic melanoma, with a sustained plateau in survival starting at approximately 3 years.[40]

There is no randomized data evaluating stopping at 2 years, however, accumulating data suggests 2 years of IO treatment may be sufficient for long term benefit. Data from Checkmate 003, a dose-escalation cohort expansion trial evaluating the safety and clinical activity of nivolumab in patients with advanced solid tumors, implemented stopping nivolumab monotherapy at 96 weeks (~ 2 years). The median follow-up was 60 months. Among the 16 participants enrolled in the NSCLC cohort, 12 participants were alive at > 5 years, did not receive further therapy after stopping nivolumab, and remained progression-free. Three of the 4 subjects that progressed prior to completion of 2 years of therapy, received subsequent therapy, and were alive at 5 years.[41]

Keynote-010, a phase 3 randomized control trial of pembrolizumab versus docetaxel for previously treated, PD-L1 positive, advanced NSCLC reported long term follow-up data. Data from participants who completed the maximum of 24 months of pembrolizumab suggests clinical benefit of pembrolizumab is durable after 2 years of treatment. The median follow-up was 2.1 years (range, 1.5 to 3 years), most participants who completed 2 years of pembrolizumab and stopped treatment were able to maintain their response, including those with stable disease and with only 4% progressed after stopping at 2 years. The OS benefit was maintained and survival plateau above 30% was noted to develop after 2 years of treatment[42], suggesting stopping therapy at 2 years did not have a clinically meaningful impact on overall survival.

Long term follow-up data from Keynote-006, a phase 3 melanoma study, demonstrates pembrolizumab provides durable efficacy after stopping at the protocol-specified 2 year treatment duration. The median follow-up in the total population was 33.9 months. Among the 104 (19%) participants who completed pembrolizumab, median exposure was 24.0 months. At a median follow-up of 9.0 months, 102 (98%) participants were alive. Responses were durable in participants who completed pembrolizumab with an estimated PFS (95% CI) of 91% (80-96) in all 104 patients, regardless of the response status.[43]

In Checkmate 153, patients who completed 1 year of nivolumab therapy were randomized to either continue or stop treatment after 1 year of therapy, with the option of retreatment upon progression. Results showed that in patients still on treatment at 1 year without progression, median PFS was significantly improved compared to those who stopped at 1 year (PFS: NR vs 10.3 months; HR=0.42 [95% CI, 0.25 to 0.71]).[44] While there was no statistically significant

difference in overall survival, there was a trend for patients on continued treatment to live longer (OS HR = 0.63 (95% CI: 0.33, 1.20), Subgroup analyses were consistent regardless whether patients had responded to therapy or had stable disease at the time of randomization. This data suggest that in previously treated advanced NSCLC, continuing treatment beyond 1 year is favorable compared to stopping treatment at 1 year. Checkmate 153 was not designed to assess 2 year duration of therapy. However, the data suggests the risk of progression after 2 years of treatment is minimal, even in the absence of further treatment. The PFS plateaus seen at 2 years from first dose include participants who stopped after 1 year.[44]

Collectively, these data suggest that there is likely no benefit from treatment beyond two years in advanced or relapsed solid tumors. Therefore, CA209817 treatment will be given for up to 2 years from start of treatment.

5.5.4 Justification for Removing Retreatment

With a prior amendment, the option for retreatment on study in subjects who progress after 2 years of treatment was removed from the protocol. Retreatment was originally included in CA209817 revised protocol 03 based on the assumption that it is biologically plausible that if a patient progresses after a checkpoint blockade agent has been discontinued, then reintroduction of the same agent could achieve tumor control, especially if the patient initially responded to treatment.

However, accumulating evidence suggests that activity of retreatment is very limited. In Checkmate 153, 34 patients stopped therapy at 1 year and were retreated upon progression. Nivolumab retreatment did not appear to re-induce responses, although tumor burden appeared to be stable over several months in some patients. However, in the majority of patients, the tumor continued to progress suggesting that treatment should be changed, using preferentially an agent or approaches with a different MOA, either as standard of care, or through clinical trials.

5.5.5 Rationale for Tumor Mutation Burden Testing

High TMB has been hypothesized to correlate with improved efficacy in patients treated with I-O therapies. This hypothesis has been supported in multiple publications across I-O therapies, tumor types, and lines of treatment. The first published study of TMB as a biomarker of clinical outcomes was reported by Snyder et al[45], where high TMB was found to be associated with efficacy in metastatic melanoma patients treated with anti-CTLA-4 therapy. Further studies by Rizvi et al (2015) reported TMB as a biomarker of pembrolizumab efficacy in second-line NSCLC patients.[14] Additional studies of pembrolizumab and atezolizumab in NSCLC have been generally consistent with these results.[46]

TMB was evaluated in an exploratory post hoc analysis in the BMS-sponsored first line NSCLC study, CheckMate 026, which represents the first phase 3 study to demonstrate the impact of TMB on efficacy of a PD-1/L1 inhibitor.[47] This analysis demonstrated that in patients with high TMB, ORR was numerically higher in the nivolumab arm versus the chemotherapy arm (47% vs 28%) and median PFS was longer in the nivolumab arm compared to the chemotherapy arm (9.7 vs 5.8 mo., HR 0.62; 95% CI 0.38, 1.00). OS was notable, though similar (18.3 vs 18.8 mo. and

1 year OS rates of 64% vs 60%, respectively), between the arms in patients with high TMB, although of note, 68% of patients in the chemotherapy arm received subsequent nivolumab.[47] Interestingly, the ORR and mPFS rates observed in the high TMB subgroup within CheckMate 026 were similar to those reported in the first line NSCLC study of pembrolizumab (Keynote-024), where ORR and mPFS were 45% and 10.3 months, respectively, in patients with ≥50% PD-L1 expression treated with pembrolizumab.[48]

Recently, the ongoing phase 3 CheckMate 227 study tested the combination of nivolumab 3mg/kg Q2W + ipilimumab 1mg/kg Q6W versus platinum-doublet chemotherapy in patients with previously-untreated metastatic or recurrent NSCLC. In the pre-specified analysis of patients with high tumor mutational burden at a prospective cutoff of ≥ 10 mutations/MB, progression-free survival was significantly longer in the group treated nivolumab plus ipilimumab compared to chemotherapy, demonstrating a median PFS of 7.2 months vs 5.5 months, respectively (HR 0.58; 97.5% CI 0.41, 0.81). The treatment effect was consistent in a pre-specified multi-variate analysis when adjusted for PD-L1 expression, histology, and other clinical factors. The ORR was also significantly greater for the nivolumab plus ipilimumab group (45.3% vs. 26.9%; treatment difference 18.4%; 95% CI (7.6, 28.8), and the responses appeared durable with 68% of responses ongoing after 1 year and the DOR not reached (95% CI 12.2, NR) compared to 5.4 months (95% CI 4.2,6.9) for chemotherapy. Among the patients with low TMB (<10 mutations/MB), no PFS benefit was observed for nivolumab plus ipilimumab compared to chemotherapy (HR 1.07; 95% CI 0.84, 1.35; mPFS 3.2mo vs 5.5mo), suggesting the use of a TMB cutoff of ≥ 10 mutations/MB was an effective biomarker.[49]

The available data to date suggest that, in addition to and independently from PD-L1 expression, TMB is also a biomarker of clinical efficacy to IO therapy.

6 STUDY POPULATION

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

6.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Participants must have signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (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 participant care.

2) Type of Participant and Target Disease Characteristics

a) Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 1. (Please see Special Population inclusion criteria in Section 6.1.1)

b) Cohort A, A1, and C (first-line NSCLC):

i) Participants with histologically confirmed Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer classification [IASLC])[50] squamous or non-squamous histology, with no prior systemic anticancer therapy

(including EGFR, ALK inhibitors, or other immuno-oncology agents) given as primary therapy for advanced or metastatic disease.

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

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

c) Cohort B (second-line NSCLC)

i) Participants with histologically- or cytologically-documented squamous or non-squamous NSCLC who present with Stage IIIB/ Stage IV disease (per IASLC), or with recurrent or progressive disease following multimodal therapy (radiation therapy, surgical resection or definitive chemoradiation therapy for locally advanced disease).

ii) Participants must have experienced disease recurrence or progression during or after one prior platinum doublet-based chemotherapy regimen for advanced or metastatic disease.

(1). Maintenance therapy following platinum doublet-based chemotherapy is not considered as a separate regimen of therapy

(2). Participants who received platinum-containing adjuvant, neoadjuvant or definitive chemoradiation therapy given for locally advanced disease, and developed recurrent (local or metastatic) disease within 6 months of completing therapy are eligible.

(3). Participants with recurrent disease > 6 months after platinum-containing adjuvant, neoadjuvant or definitive chemoradiation therapy given for locally advanced disease, who also subsequently progressed during or after a platinum doublet-based regimen given to treat the recurrence, are eligible.

d) Evaluable disease by computed tomography (CT) or magnetic resonance imaging (MRI); radiographic tumor assessment performed within 28 days of start of study treatment.

e) Cohorts A, A1, and B: Participants must have tissue submitted for PD-L1 immunohistochemical (IHC) testing prior to the treatment assignment. If PD-L1 results are available from another BMS study, or a commercially available complementary diagnostic using an acceptable antibody (ie, 28-8, 22-C3, SP263), these results are acceptable. PD-L1 results obtained using antibody SP142 are not acceptable.

i) Either a formalin-fixed, paraffin-embedded (FFPE) tissue block or unstained tumor tissue sections, with an associated pathology report, must be submitted for biomarker evaluation prior to treatment assignment. The tumor tissue sample may be fresh or archival if obtained within 12 months prior to enrollment (6 months for slides).

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

(1). Samples collected via other procedures, including, but not limited to, endobronchial ultrasound (EBUS) guided biopsy, transbronchial lung biopsy

(TBLB) may be approved by the BMS medical monitor (MM)/study director (SD) on a case by case basis.

iii) Sufficient tissue (10-15 unstained slides) must be available.

f) Prior palliative radiotherapy to non-central nervous system (CNS) lesions must have been completed at least 2 weeks prior to the treatment assignment. Participants with symptomatic tumor lesions at baseline that may require palliative radiotherapy within 4 weeks of the treatment assignment are strongly encouraged to receive palliative radiotherapy prior to starting study therapy. Lesions which have received or are anticipated to receive palliative RT may not be designated as target or non-target lesions in the baseline tumor assessment.

g) Cohort C Tissue requirements: Sufficient tissue (10 unstained slides ≤ 3 months old) must be available for prospective TMB testing. Previously generated TMB results from the Foundation Medicine TMB test confirming ≥ 10 mutations/MB are acceptable. TMB testing results are required for enrollment. Five additional unstained slides for must also be available for PD-L1 testing. However, if PD-L1 results are available from another BMS study, or a commercially available Dako 28-8 complementary diagnostic using an acceptable antibody (ie, 28-8, 22-C3, SP263), these results are acceptable. PD-L1 results obtained using antibody SP142 are not acceptable. EGFR mutation and ALK translocation status will be assessed locally.

3) Age and Reproductive Status

a) Males and Females, ages 18 (or age of majority) and older.

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

c) Women must not be breastfeeding.

d) Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception for the duration of treatment with study treatment(s) nivolumab and ipilimumab plus 5 half-lives of study treatment 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 (Appendix 4) for the duration of treatment with study treatment(s) nivolumab and ipilimumab plus 5 half-lives of the study treatment plus 90 days (duration of sperm turnover) for a total of 7 months post-treatment completion. In addition, male participants 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.

g) Post-menopausal females under age 55 must have serum FSH levels > 40 mIU (see Appendix 4)

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

pregnancy. Investigators shall advise on the use of highly effective methods of contraception, (Appendix 4) which have a failure rate of < 1% when used consistently and correctly.

6.1.1 Inclusion Criteria for Cohort A1 Special Population

4) Participants may be included in the 1L NSCLC special population cohort of the study with one of the following criteria. All other inclusion and exclusion criteria apply.

a) ECOG PS 0 and 1 participants with untreated, asymptomatic brain metastases
   i) Participants with untreated brain metastases must not require corticosteroids or anticonvulsant therapy.

b) ECOG PS 0 and 1 participants with hepatic impairment, defined as follows:
   i) Total bilirubin = 1.5-3.0 x ULN, and/or;
   ii) AST/ALT = 3-5 x ULN

c) ECOG PS 0 and 1 participants with renal impairment, defined as follows:
   i) Creatinine clearance 20-39 mL/min (Cockcroft-Gault formula)

d) ECOG PS 0 and 1 participants with HIV
   i) Participants who are HIV positive must meet the following criteria:
      (1). Acute or Chronic HIV infection. HIV-1 infection as documented by HIV rapid test performed in conjunction with screening (or ELISA, test kit, and confirmed by Western blot or other approved test). HIV plasma HIV-1 RNA below detected limit (limit of detection: 75) within 4 weeks prior to registration, without confirmed viral breakthrough for at least 6 months.
      (2). HIV plasma HIV-1 RNA below detected limit (limit of detection: 75) within 4 weeks prior to registration, without confirmed viral breakthrough for at least 6 months.
      (3). Participants with Chronic HIV must be asymptomatic/clinically latent, with CD4+ count of > 200 cells/mm^3 obtained within 2 weeks prior to enrollment.
      (4). Participants with a diagnosis of AIDS are excluded.

e) Participants with ECOG PS 2 who, in the opinion of the investigator, are expected to be able to tolerate study treatment.

6.2 Exclusion Criteria

1) Target Disease Exceptions

a) Participants with known EGFR mutations which are sensitive to available targeted inhibitor therapy (including, but not limited to, deletions in exon 19 and exon 21 [L858R] substitution mutations) are excluded. All participants with non-squamous histology must have been tested for EGFR mutation status, with the exception of participants with known KRAS mutations. Use of an FDA-approved EGFR test is strongly encouraged. Participants with non-squamous histology and unknown or indeterminate EGFR status are excluded.

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

2) Medical Conditions

a) Participants with untreated CNS metastases are excluded.

i) Participants are eligible if CNS metastases are adequately treated and participants are neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to treatment assignment. In addition, participants must be either off corticosteroids, or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent) for at least 2 weeks prior to treatment assignment.

b) Participants with carcinomatous meningitis.

c) Participants must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before treatment assignment.

d) Active malignancy requiring concurrent intervention.

e) Participants with an active, known or suspected autoimmune disease. Participants 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.

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

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

h) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)-with the exceptions noted for Cohort A1 participants. See Appendix 9

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

3) Prior/Concomitant Therapy

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

b) **Not applicable per Revised Protocol 04**: *Cohort B: Prior participation in a BMS study where participants were treated with nivolumab and/or ipilimumab, except when approved by Medical Monitor/Study Director*

c) 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. 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

4) Physical and Laboratory Test Findings for Cohorts A, B, and C

Please see Section 6.1.1 Inclusion Criteria for Cohort A1 Special Population for physical and laboratory test findings

a) White blood cells (WBC) < 2000/μL
b) Neutrophils < 1500/μL
c) Platelets < $100*10^3$/μL
d) Hemoglobin < 9.0 g/dL
e) Serum creatinine > 1.5 x ULN, unless creatinine clearance ≥ 40 mL/min (measured or calculated using the Cockroft-Gault formula)
f) Aspartate aminotransferase (AST)/ alanine aminotransferase (ALT): > 3.0 x ULN
g) Total bilirubin > 1.5 x ULN (except participants with Gilbert Syndrome who must have a total bilirubin level of < 3.0x ULN)
h) Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic infection.

5) Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to study drug components.

6) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: under certain specific circumstances a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply and Bristol-Myers Squibb approval is required.
b) Participants 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 participants and that the results of the study can be used. It is imperative that participants fully meet all eligibility criteria.

6.3 Lifestyle Restrictions

Not applicable. No restrictions are required

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any serious AEs.

6.4.1 Retesting During Screening or Lead-In Period

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

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).

The most current result prior to Treatment assignment is the value by which study inclusion will be assessed, as it represents the participant's most current clinical state.

Laboratory parameters and/or assessments that are included in Table 2-1, Screening Procedural Outline may be repeated in an effort to find all possible well-qualified participants. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

7 TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo or medical device intended to be administered to a study participant according to the study treatment assignment or treatment allocation. Study treatment includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) and consist of the following:

- Nivolumab
- Ipilimumab

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.

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.

Table 7-1: Study treatments for CA209817					
Product Description / Class and Dosage Form	**Potency**	**IP/ Non-IMP**	**Blinded or Open Label**	**Packaging / Appearance**	**Storage Conditions (per label)**
Nivolumab/BMS - 936558-01 Solution for Injection	10 mg/ml	IP	Open Label	240 mg kit or 5 or 10 (100mg) vials per carton; Clear to opalescent, colorless to pale yellow liquid; Few particulates may be present.	Store at 2-8°C; Protect from light and freezing.
Ipilimumab Solution for Injection	5 mg/ml	IP	Open Label	4 vials per carton; Clear, colorless liquid. Few particles may be present.	Store at 2-8°C; Protect from light and freezing.

7.1 Treatments Administered

The selection and timing of dose for each participant is as follows:

Table 7.1-1: Selection and Timing of Dose

Study Treatment	Unit dose strength(s)/Dosage level(s)	Dosage formulation Frequency of Administration	Route of Administration
Nivolumab	240 mg	Every 2 weeks	IV
Ipilimumab	1 mg/kg	Every 6 weeks	IV

Participants will receive treatment with nivolumab 240 mg as a 30 minute infusion every 2 weeks and ipilimumab 1 mg/kg as a 30 minute infusion every 6 weeks, starting on Day 1, until progression, unacceptable toxicity, withdrawal of consent, 24 months from first dose, or the study ends, whichever occurs first. Participants should begin study treatment within 3 calendar days of treatment assignment.

When nivolumab and ipilimumab are to be administered on the same day, nivolumab is to be administered first. Nivolumab infusion must be promptly followed by a flush of diluent to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be the ipilimumab study treatment and will start after the infusion line has been flushed, filters changed and patient has been observed to ensure no infusion reaction has occurred.

Nivolumab and ipilimumab may be diluted in 0.9% Sodium Chloride solution or 5% Dextrose solution.

Dosing calculations for ipilimumab should be based on the body weight. If the participant's weight on the day of dosing differs by > 10% from the weight used to calculate the prior dose, the dose must be recalculated. All doses should be rounded to the nearest milligram. There will be no dose modifications allowed.

There are no premedications recommended.

Participants should be carefully monitored for infusion reactions. If an acute infusion reaction is noted, participants should be managed according to Section 7.4.3.

Doses of nivolumab and/or ipilimumab may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. For more details, see Sections 7.4.1 (dose delays), 7.4.3 (resuming treatment), and 8.1 (discontinuation).

7.2 Method of Treatment Assignment

All participants will be centrally assigned to treatment using an Interactive Response Technology (IRT). Before the study is initiated, each user will receive log in information and directions on how to access the IRT. Study treatment will be dispensed at the study visits as listed in Schedule of Activities (Section 2).

7.3 Blinding

Not applicable. This is an open-label study, and therefore blinding procedures are not applicable.

7.4 Dosage Modification

7.4.1 Dose Delay Criteria for Cohorts A, B, and C

Nivolumab and ipilimumab administration should be delayed for the following:

- Grade 2 non-skin, drug-related AE, except for fatigue
- Grade 3 skin, drug-related AE
- Grade 2 drug-related creatinine, AST, ALT and/or total bilirubin abnormalities
- Grade ≥3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require a dose delay
  - Grade ≥ 3 AST, ALT, Total Bilirubin will require dose discontinuation
- Any AE, laboratory abnormality or inter-current illness which, in the judgment of the investigator, warrants delaying the dose of study medication.
- Participants receiving ipilimumab in combination with nivolumab that have drug-related toxicities that meet the criteria for dose delay, should have both drugs (ipilimumab and nivolumab) delayed until retreatment criteria are met. (Exceptions apply to the retreatment criteria after dose delay of ipilimumab and nivolumab for Grade 4 amylase and lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and that are attributed to ipilimumab alone.)

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

Rescheduling:

- Nivolumab may be delayed until the next planned ipilimumab dose if the next ipilimumab dose is scheduled within the next 12 days. This will permit periodic ipilimumab dosing to be synchronized with nivolumab dosing.

- Ipilimumab should be dosed at the specified interval regardless of any delays in intervening nivolumab doses. However, in order to maintain periodic synchronized dosing of ipilimumab and nivolumab, the dosing days of nivolumab and ipilimumab may be adjusted within the permitted ± 5 day window, as long as consecutive nivolumab doses are given at least 12 days apart. Ipilimumab may be delayed beyond the 5 day window if needed to synchronize with the next nivolumab dose.
- If an ipilimumab dose is delayed beyond 6 weeks from the prior ipilimumab dose, then subsequent ipilimumab doses should rescheduled to maintain the 6 week interval between consecutive ipilimumab doses.
- A dose delay of ipilimumab which results in no ipilimumab dosing for > 12 weeks requires ipilimumab discontinuation, with exceptions as noted in Section 8.1.1.2.

7.4.1.1 Dose Delay Criteria for Special Population (Cohort A1)

All dose delay criteria listed in Section 7.4.1 apply to the special population cohort, with the following exceptions for participants with hepatic and renal impairment:

- If a participant has Grade 2 baseline AST or ALT elevation (> 3.0-5.0 x ULN), delay dosing for a two-fold increase in AST or ALT or for AST or ALT values 8 x ULN.
- If a participant has Grade 2 baseline total bilirubin (> 1.5-3.0 x ULN), delay dosing for drug-related elevation > 5.0 x ULN.
- If a participant has Grade 4 CrCl (CrCl < 15 ml/min), delay dosing/hold dose; participants may resume dosing with CrCl > 20 ml/min.

7.4.2 Dose Reductions

There will be no dose reductions for nivolumab or ipilimumab.

7.4.3 Treatment of Infusion Reactions

Since nivolumab and ipilimumab contain only human immunoglobulin protein sequences, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as an SAE if criteria are met. Infusion reactions should be graded according to National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE) (Version 4) guidelines.

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

For Grade 1 symptoms: (mild reaction; infusion interruption not indicated; intervention not indicated)

- Remain at bedside and monitor participant until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg

(or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional nivolumab or ipilimumab administrations.

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

- Stop the nivolumab or ipilimumab infusion, begin an IV infusion of normal saline (or diluent), and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor participant 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 participant closely. If symptoms recur, then no further nivolumab or ipilimumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the participant until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF).
- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before nivolumab or ipilimumab infusions. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

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

- Immediately discontinue infusion of nivolumab or ipilimumab. Begin an IV infusion of normal saline (or diluent) and treat the participant 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. Participant should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab or ipilimumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant 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).

7.4.4 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 and ipilimumab are considered immuno-oncology agents in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Management Algorithms have been developed to assist investigators in assessing and managing the following groups of AEs:

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

The above algorithms are found in both the nivolumab and ipilimumab Investigator Brochures, as well as in Appendix 7.

Additionally, rare cases of myotoxicity (myositis, myocarditis, and rhabdomyolysis), some with fatal outcome, have been reported with nivolumab or nivolumab in combination with ipilimumab. If a patient develops signs and symptoms of myotoxicity, close monitoring should be implemented, and the patient referred to a specialist for assessment and treatment without delay. Based on the severity of myotoxicity, nivolumab or nivolumab in combination with ipilimumab should be withheld or discontinued, and appropriate treatment instituted. For grade 3 myocarditis, nivolumab or nivolumab in combination with ipilimumab should be permanently discontinued.

7.4.5 Criteria to Resume Dosing

7.4.5.1 Criteria to Resume Nivolumab for Cohorts A, B, and C

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

- Participants may resume treatment in the presence of Grade 2 fatigue.
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- Participants with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin.
- Participants with combined Grade 2 AST/ALT and total bilirubin values meeting discontinuation parameters (Section 8.1) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a

steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the BMS Medical Monitor.

- Participants who received systemic corticosteroids for management of any drug-related toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone ≤ 10 mg/day.

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

Dose delay of nivolumab which results in treatment interruption of > 6 weeks requires treatment discontinuation, with exceptions as noted in Section 8.1.1.

7.4.5.2 Criteria to Resume Ipilimumab for Cohorts A, B, and C

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

- Participants may resume treatment in the presence of Grade 2 fatigue.
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- Participants with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT or total bilirubin.
- Participants with combined Grade 2 AST/ALT and total bilirubin values meeting discontinuation parameters (Section 8.1) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed.
- Participants who received systemic corticosteroids for management of any drug-related toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone ≤ 10 mg/day.
- Drug-related endocrinopathies (except Grade 3 or greater adrenal insufficiency) adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor
- Dose delay of ipilimumab which results in no ipilimumab dosing for > 12 weeks requires ipilimumab discontinuation, with exceptions as noted in Section 8.1.1.2.
- Ipilimumab may not be resumed sooner than 37 days after the prior ipilimumab dose.
- In general, participants who meet criteria to resume ipilimumab will also have met criteria to resume nivolumab, so it should be feasible to synchronize dosing of both drugs when resuming ipilimumab. In order to facilitate this, the dosing days of nivolumab and ipilimumab may be adjusted within the permitted ± 5 day window, as long as consecutive nivolumab doses are given at least 12 days apart.

One exception to note is when ipilimumab and nivolumab doses are delayed due to drug-related Grade 4 amylase or lipase abnormalities not associated with symptoms or clinical manifestations of pancreatitis. If the investigator assesses the Grade 4 amylase or lipase abnormality to be related to ipilimumab and not related to nivolumab, nivolumab may be resumed when the amylase or lipase abnormality resolves to Grade ≤ 3 but ipilimumab may only be resumed when the amylase or lipase abnormality resolves to Grade 1 or baseline. Investigator attribution of this toxicity to the ipilimumab dosing must be clearly noted in the participant's medical chart. The BMS Medical Monitor should be consulted prior to resuming nivolumab in such participants.

See Section 8 for treatment discontinuation criteria.

Please see Section 7.4.5.3 Criteria to Resume Nivolumab or Ipilimumab for Special Population.

7.4.5.3 Criteria to Resume Nivolumab and Ipilimumab for Special Population (Cohort A1)

The criteria to resume nivolumab and ipilimumab dosing described in Section 7.4.5.1 and Section 7.4.5.2 apply to special population participants, with the following exceptions for hepatic impairment:

- Participants with Grade 2 baseline AST or ALT elevation (> 3.0-5.0 x ULN), who require dose delays for reasons other than drug-related AST or ALT elevation > 8 x ULN, may resume dosing in the presence of AST or ALT elevation ≤ 8 x ULN.
- Participants with Grade 2 baseline total bilirubin (> 1.5-3.0 x ULN), who require dose delays for reasons other than drug-related total bilirubin elevation > 5.0 x ULN, may resume dosing in the presence of total bilirubin elevation ≤ 5.0 x ULN.

Participants with combined AST/ALT and total bilirubin values meeting discontinuation parameters (Section 8.1) should have treatment permanently discontinued.

7.5 Preparation/Handling/Storage/Accountability

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 Participants. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

The product storage manager should ensure that the study treatment 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 treatment arise, the study treatment should not be dispensed and contact BMS immediately.

Study treatment 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).

- Required storage conditions for nivolumab and ipilimumab are provided in Table 7-1.
- Further guidance on preparation of nivolumab and ipilimumab for infusion will be provided in a separate Pharmacy Manual.

Further guidance and information for final disposition of unused study treatment are provided in Appendix 2.

7.5.1 Retained Samples for Bioavailability / Bioequivalence

Not Applicable.

7.6 Treatment Compliance

Study treatment compliance will be periodically monitored by drug accountability. Drug accountability should be reviewed by the site study staff at each visit to confirm treatment compliance. Sites should discuss discrepancies with the participant at each on-treatment study visit.

7.7 Concomitant Therapy

7.7.1 Prohibited and/or Restricted Treatments

Prohibited and/or restricted medications taken prior to study drug administration in the study are described below. Medications taken within 14 days prior to study drug administration must be recorded on the CRF.

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 7.7.2)
- Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of the disease under study). Allowable palliative radiation is described in Section 7.7.2.1.
- 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.

Any concomitant therapies taken at any time during the study must be recorded on the CRF.

7.7.2 Other Restrictions and Precautions

Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of treatment assignment 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.

7.7.2.1 Palliative Radiotherapy (All Cohorts)

On study palliative radiotherapy is not allowed on target lesions used to assess disease response and designated as such in the eCRF. Non-target bone lesions not so designated and that do not include lung tissue in the planned radiation field may be treated with palliative radiotherapy at any time while participants remain on study treatment. In addition, palliative radiotherapy to a single metastatic site, other than bone, is permitted in participants who do not require immediate initiation of second line systemic anti-cancer therapy. Such radiotherapy to non-bone lesions must not be given within 2 weeks of initiation of study therapy and such lesions are not permitted to be designated as baseline target lesions in the eCRF. Details of palliative radiotherapy should be documented in the source records and CRF. Details in the source records should include: dates of treatment, anatomical site, dose administered and fractionation schedule, and AEs.

Participants requiring palliative radiotherapy to designated target lesions must be discontinued from study therapy. Participants requiring palliative radiotherapy should be carefully assessed for disease progression. Participants considered as having progressive disease are required to discontinue study therapy, unless eligible to continue treatment beyond progression per the guidance in Section 8.1.2.

7.7.3 Permitted Therapy

Participants 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.

7.8 Treatment After the End of the Study

At the end of the study, BMS will not continue to provide BMS supplied study treatment to participants/investigators unless BMS chooses to extend the study. The investigator should ensure that the participant receives appropriate standard of care to treat the condition under study.

BMS reserves the right to terminate access to BMS supplied study treatment if any of the following occur: a) the study is terminated due to safety concerns; b) the development of nivolumab and/or ipilimumab is terminated for other reasons, including but not limited to lack of efficacy and/or not meeting the study objectives; c) the participant can obtain medication from a government sponsored or private health program. In all cases BMS will follow local regulations.

8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

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

- Participant's request to stop study treatment. Participants who request to discontinue study treatment 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 participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information
- Any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Termination of the study by 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

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

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

8.1.1 Study Drug Discontinuation

8.1.1.1 Nivolumab Discontinuation for Cohorts A, B, and C

Nivolumab treatment should be permanently discontinued for the following:

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

- Grade 3 drug-related endocrinopathies, adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
- Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
  - ♦ Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
  - ♦ Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
    - o Grade ≥ 3 drug-related AST, ALT or Total Bilirubin requires discontinuation*
    - o Concurrent AST or ALT > 3 x ULN and total bilirubin > 2x ULN

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

- Any Grade 4 drug-related adverse event or laboratory abnormality (including but not limited to creatinine, AST, ALT, or Total Bilirubin), except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 drug-related endocrinopathy adverse events, such as, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor.
- Any event that leads to delay in dosing lasting > 6 weeks for nivolumab 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 for nivolumab from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor (or designee).

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

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

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

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

If a participant meets criteria for discontinuation and investigator is unable to determine whether the event is related to both or one study drug, the participant should discontinue both nivolumab and ipilimumab and be taken off the treatment phase of the study. Continuation of ipilimumab after discontinuation of nivolumab is not allowed on study.

8.1.1.2 Ipilimumab Dose Discontinuation for Cohorts A, B, and C

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

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks OR requires systemic treatment;
- Any Grade ≥ 3 bronchospasm or other hypersensitivity reaction;
- Any other Grade 3 non-skin, drug-related adverse event with the following exceptions for laboratory abnormalities, grade 3 nausea and vomiting, grade 3 neutropenia and thrombocytopenia, and symptomatic endocrinopathies (except for adrenal insufficiency) which resolved (with or without hormone substitution);
- Any drug-related LFT abnormality that meets the following criteria require discontinuation:
- AST or ALT > 8x ULN
- Total bilirubin > 5 x ULN
- Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Any Grade 4 drug-related AE or laboratory abnormality, except for the following events, which do not require discontinuation:
- Grade 4 neutropenia ≤ 7 days
- Grade 4 lymphopenia or leukopenia
- Isolated Grade 4 amylase or lipase abnormalities which are not associated with symptoms or clinical manifestations of pancreatitis. The BMS Medical Monitor should be consulted for Grade 4 amylase or lipase abnormalities.
- Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
- Grade 4 drug-related endocrinopathy AEs such as hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone

replacement (corticosteroids, thyroid hormones) or glucose controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor.

- Any treatment delay resulting in no ipilimumab dosing for > 12 weeks with the following exceptions: Dosing delays to manage drug-related AEs, such as prolonged steroid tapers, are allowed. Prior to re-initiating treatment in a participant with a dosing delay lasting > 12 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.
- Dosing delays resulting in no ipilimumab dosing for > 12 weeks that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor. Prior to re-initiating treatment in a participant with a dosing delay lasting > 12 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued ipilimumab dosing.

8.1.1.3 Nivolumab and Ipilimumab Dose Discontinuation for Special Population (Cohort A1)

The dose discontinuation criteria described in Section 8.1.1.1 and Section 8.1.1.2 apply to special population participants, with the following exceptions for hepatic impairment:

- Any liver function test (LFT) abnormality that meets the following criteria require discontinuation (also see Hepatic Adverse Event Management Algorithm):
  - AST or ALT > 10 x ULN for > 2 weeks
  - AST or ALT > 15 x ULN
  - Total bilirubin > 8 x ULN
  - Concurrent AST or ALT > 3 x ULN and total bilirubin > 5 x ULN
- Any drug-related renal dysfunction

Participants requiring renal transplant must be discontinued from study therapy. In some cases, participants requiring dialysis may be permitted to continue study therapy; however, these cases must be reviewed and approved by the BMS Medical Monitor.

8.1.2 Disease Progression

In general, study treatment must be discontinued at the time of disease progression per Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria. However, accumulating evidence indicates a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease.[36]

Participants may be permitted to continue study treatment with nivolumab (with or without ipilimumab) beyond initial RECIST 1.1 defined progressive disease, assessed by the investigator

up to a maximum of 24 months from date of first dose, upon approval by the BMS Medical Monitor or Study Director, as long as they meet the following criteria:

- Investigator-assessed clinical benefit.
- Tolerance of study drug
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
- Participant provides written informed consent prior to receiving additional nivolumab treatment. All other elements of the main consent including description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply.

A radiographic assessment/ scan should be performed within 6 weeks of initial investigator-assessed progression to determine whether there has been a decrease in the tumor size or continued progressive disease. The assessment of clinical benefit should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued treatment with nivolumab.

If the investigator feels that the nivolumab participant continues to achieve clinical benefit by continuing treatment, the participant should remain on the trial and continue to receive monitoring according to the Schedule of Activities in Section 2.

For the participants who continue nivolumab study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden with a minimum 5 mm absolute increase from time of initial progressive disease. This includes an increase in the sum of diameters of all target lesions and/ or the diameters of new measurable lesions compared to the time of initial progressive disease. Nivolumab treatment should be discontinued permanently upon documentation of further progression.

New lesions are considered measureable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). Any new lesion considered non-measureable at the time of initial progression may become measureable and therefore included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of new lesions which become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

8.1.3 Additional Guidance on Treatment Discontinuation

Discontinuation of the study treatment for abnormal liver tests should be considered by the investigator when a participant meets one of the conditions outlined in Section 7.4.1 OR Appendix 7 or if the investigator believes that it is in best interest of the participant. Discontinuation is required if the participants meets one of the conditions described in Section 8.1.

Refer to the Schedule of Activities for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed

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 participant becomes pregnant during a clinical trial, the study treatment must be discontinued immediately. In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Please call the BMS 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 treatment, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

All participants who discontinue study treatment should comply with protocol specified follow-up procedures as outlined in Section 2. The only exception to this requirement is when a participant withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

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

8.1.4 Post Study Treatment Study Follow-up

In this study, overall survival is a key secondary endpoint of the study. Post study follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study treatment 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.

8.2 Discontinuation from the Study

Participants who request to discontinue study treatment 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 participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.

- Participants 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 treatment 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 participant 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.

- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.3 Lost to Follow-Up

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of **three** documented phone calls, faxes, or emails as well as lack of response by participant to one registered mail letter. All attempts should be documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain 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 participant's informed consent, then the investigator may use a Sponsor retained third-party representative to assist site staff with obtaining participant'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 participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities (Section 2).
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before treatment assignment. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities.

Additional measures beyond those described in Section 2, including non-study required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug induced liver enzyme evaluations) will be monitored during the follow-up phase via on site/local labs until all study drug related toxicities resolve, return to baseline, or are deemed irreversible.

If a participant shows pulmonary-related signs (hypoxia, fever) or symptoms (eg. dyspnea, cough, fever) consistent with possible pulmonary AEs, the participant should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm in the BMS-936558 (nivolumab) Investigator Brochure and Appendix 7.

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

9.1 Efficacy Assessments

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

Study evaluations will take place in accordance with the Schedule of Activities (Section 2), according to RECIST 1.1 criteria.[51] CT with oral/IV contrast or contrast-enhanced MRI is the preferred imaging modalities for assessing radiographic tumor response. If a participant has a known allergy to contrast material, please use local prophylaxis standards to obtain the assessment with contrast if at all possible, or use the alternate modality. In cases where contrast is strictly contraindicated, a non-contrast scan will suffice. Screening assessments should be performed within 42 days of start of study treatment. Brain MRI is the preferred imaging method for evaluating CNS metastasis, and assessment is required during screening in participants with a known history of treated brain metastases. All known or suspected sites of disease (including CNS) should be assessed at screening and 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, positron emission tomography (PET) scan, or ultrasound are not adequate for assessment of RECIST response. In selected circumstances where such modalities are the sole modality used to assess certain non-target organs, those non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected. Previously treated CNS metastases are not considered measurable lesions for purposes of RECIST determined response. Participants with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated.

Radiographic tumor assessments will be conducted until disease progression (or until discontinuation of study therapy in participants receiving study drug beyond progression), lost to follow-up, or withdrawal of study consent. Tumor assessments for all participants should continue as per protocol even if dosing is interrupted. Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible. Changes in tumor measurements and tumor responses to guide ongoing study treatment decisions will be assessed by the investigator using RECIST 1.1 (Appendix 6).

9.1.1 Imaging Assessment for the Study

At the Sponsor's discretion, de-identified scans and measurements may be collected and reviewed by independent radiologists using RECIST 1.1 criteria at a later date, or at any time during the study.

9.2 Adverse Events

The definitions of an AE or serious adverse event (SAE) can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue before completing the study.

Contacts for SAE reporting specified in Appendix 3

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.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

The collection of non-serious AE information should begin at initiation of study treatment until 100 days after the last dose of study therapy, at the timepoints specified in the Schedule of Activities (Section 2). Non-serious 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 participants.

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of SAEs for expedited reporting. Following the participant'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 after discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

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

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the eCRF section.
- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in Appendix 3.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of this being available.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

The method of evaluating, and assessing causality of AEs and SAEs and the procedures for completing and reporting/transmitting SAE reports are provided in Appendix 3.

9.2.2 Method of Detecting AEs and SAEs

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

9.2.3 Follow-up of AEs and SAEs

- Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Appendix 3).
- Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment as appropriate.
- All identified non-serious AEs must be recorded and described on the non-serious 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.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 9.2 will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3).

Further information on follow-up procedures is given in Appendix 3.

9.2.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a product under clinical investigation are met.
- An investigator who receives an investigator safety report describing SAEs or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

Sponsor or designee will be reporting AEs to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320. A SUSAR (Suspected, Unexpected Serious Adverse Reaction) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements. All SAEs must be collected that occur during the screening period and within 100 days of the last dose of study treatment. For participants randomized/assigned to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of treatment assignment.

9.2.5 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant 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 Appendix 3.

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

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

Any pregnancy that occurs in a female partner of a male study participant should be reported to Sponsor or designee. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

9.2.6 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the non-serious 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 participant to have study treatment discontinued or interrupted
- Any laboratory test result abnormality that required the participant 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).

9.2.7 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 9.2 and Appendix 3 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 aminotransaminase (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.

9.2.8 Other Safety Considerations

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

9.3 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 9.2).

In the event of an overdose the investigator/treating physician should:

1) Contact the Medical Monitor immediately
2) Closely monitor the participant for AEs/SAEs and laboratory abnormalities
3) Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

9.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities. Safety assessments include AEs, physical examinations, vital signs, ECOG performance status, assessment of signs and symptoms, laboratory tests, and pregnancy tests as outlined in the Schedule of Activities.

9.4.1 Electrocardiograms

Refer to Schedule of Activities. A 12-lead ECG must be performed during the screening phase, preferably after eligibility has been confirmed. This will serve as a baseline assessment in the event of any on-study cardiac AEs. Vital signs should also be taken as per institutional standard of care prior to, during and after infusions.

9.4.2 Clinical Safety Laboratory Assessments

- Investigators must document their review of each laboratory safety report.
- All clinical safety laboratory assessments will be performed locally per the Schedule of Activities and Table 9.4.2-1.

Table 9.4.2-1: Laboratory Assessment Panels

Hematology	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Serum Chemistry	
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Alkaline phosphatase Creatinine Blood Urea Nitrogen (BUN) or Serum Urea Level Glucose Uric acid	Sodium Potassium Chloride Calcium Phosphate Lipase Amylase TSH (reflex to free T3 and T4 if abnormal) Creatinine clearance (CrCL) calculation using Cockcroft-Gault at screening only and every 6 weeks for participants with renal impairment.
Serology	
Serum for hepatitis C antibody or hepatitis C RNA, hepatitis B surface antigen (screening only) When mandated locally, HIV testing must be performed. HIV testing is required for all participants in Germany	

Table 9.4.2-1: Laboratory Assessment Panels
(see Appendix 9).
Other Analyses
Pregnancy test and FSH (WOCBP only, as described in Section 2).

9.4.3 Imaging Safety Assessment

Not Applicable.

9.5 Pharmacokinetic Assessment

Samples for PK and immunogenicity assessments will be collected for all participants receiving nivolumab and ipilimumab as described in Table 9.5.1-1. 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.

9.5.1 Pharmacokinetic and Immunogenicity Collection and Processing: All Cohorts

A detailed schedule of PK and immunogenicity evaluations is provided in Table 9.5.1-1. PK samples will be analyzed for nivolumab/ipilimumab by a validated ligand binding assay. Immunogenicity samples will be analyzed for anti-nivolumab antibodies/anti-ipilimumab antibodies by a validated immunogenicity assay; samples may also be analyzed for neutralizing antibodies by a validated method. Serum samples may be analyzed by an exploratory method that measures anti-drug antibodies for technology exploration purposes; exploratory results will not be reported. Serum samples designated for PK or biomarker 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 9.5.1-1: Pharmacokinetic and Immunogenicity Sample Collection for Nivolumab and Ipilimumab (All Cohorts)

Study Day[a] (1 Cycle = 6 weeks)	Event (Relative To Dosing) Hour	Time (Relative To Dosing) Hour: Min	PK Blood Sample for Nivolumab	IMG Blood Sample for Nivolumab	PK Blood Sample for Ipilimumab	IMG Blood Sample for Ipilimumab
C1D1 (Nivolumab + Ipilimumab dose 1)	Predose[b]	00:00	X	X	X	X
C1D1	0.5 (EOI)[c]	00:30[c]	X		X	
C1D15 [d] (Nivolumab dose 2)	Predose[b]	00:00	X	X	X	X

Table 9.5.1-1: Pharmacokinetic and Immunogenicity Sample Collection for Nivolumab and Ipilimumab (All Cohorts)

Study Day[a] (1 Cycle = 6 weeks)	Event (Relative To Dosing) Hour	Time (Relative To Dosing) Hour: Min	PK Blood Sample for Nivolumab	IMG Blood Sample for Nivolumab	PK Blood Sample for Ipilimumab	IMG Blood Sample for Ipilimumab
C2D15 [d] (Nivolumab dose 5)	Predose[b]	00:00	X	X	X	X
C4D15 [d] (Nivolumab dose 11)	Predose[b]	00:00	X	X	X	X
D15 of every 4th cycle after C4D15 until discontinuation of study treatment or maximum up to 2 years of treatment [d]	Predose[b]	00:00	X	X	X	X

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

[b] Predose samples should be collected just before the administration of the first drug (preferably within 30 minutes). 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.

[c] EOI: End of Infusion. This sample should be taken immediately prior to stopping the second drug infusion (preferably within 2 minutes prior to the end of infusion). If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly. EOI samples may not be collected from the same IV access as drug was administered.

[d] If the D15 PK collection is missed, PK can be collected at next visit, D29.

9.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.7 Pharmacogenomics

Pharmacogenomic testing will not be performed in this study.

9.8 Biomarkers

9.8.1 Tumor Tissue Specimens

9.8.1.1 Cohorts A, A1,and B

Fresh or archival FFPE tumor tissue collected within 12 months (block) or within 6 months for sectioned slides) must be submitted for PD-L1 IHC testing prior to the treatment assignment for all cohorts. Previously generated PD-L1 results are also acceptable if generated using anti-PD-L1 antibodies 28-8, 22-C3 or SP263. If results using approved antibodies are provided, then additional PD-L1 testing is not required. PD-L1 results generated using the SP142 antibody are not acceptable. If PD-L1 status is unknown then samples will be sent to a third party to stain and

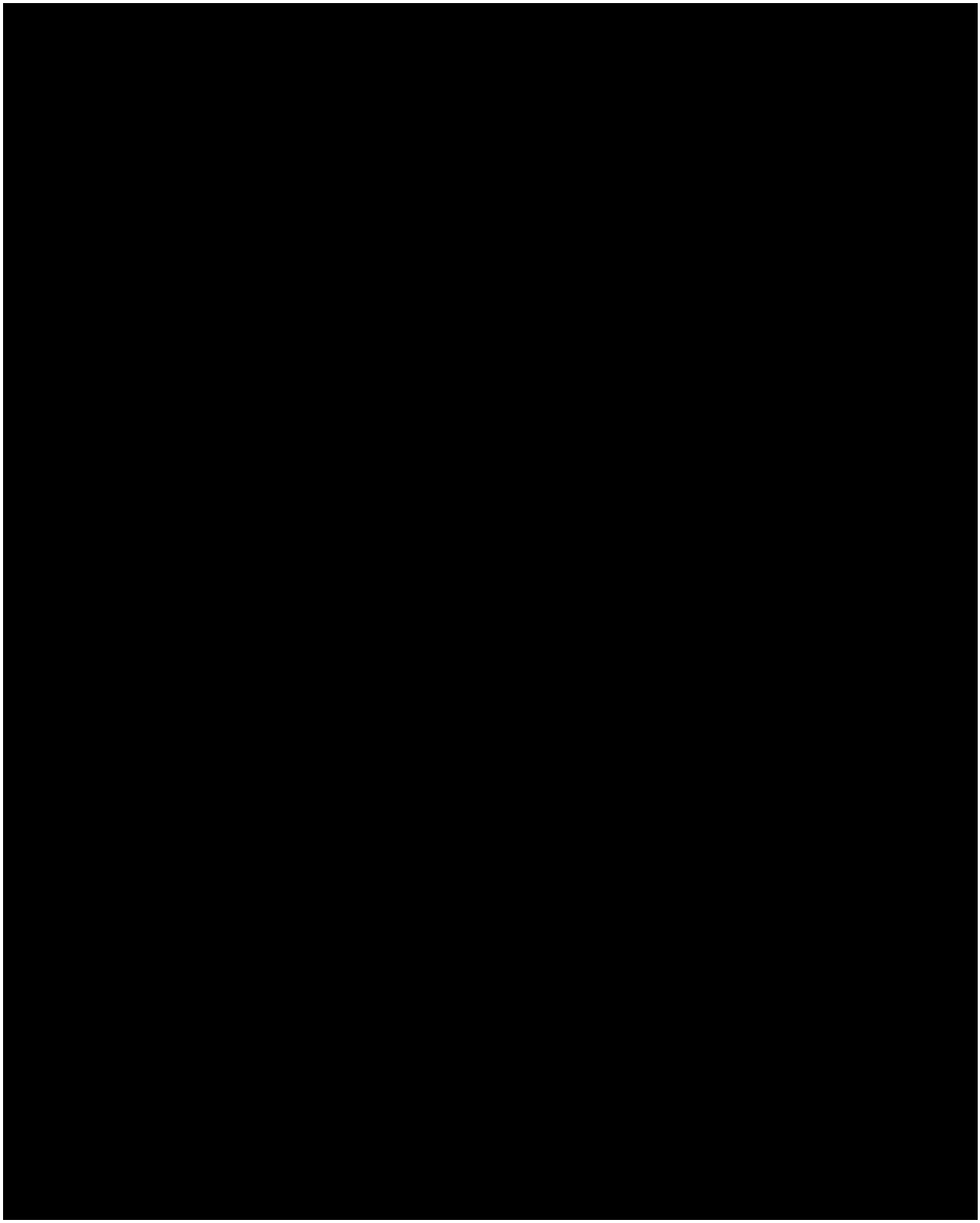
score for PD-L1 expression using the PD-L1 IHC 28-8 pharmDx kit (Dako). Stained tissue samples will be assessed by a pathologist at a central lab identified by the Sponsor and scored as PD-L1 expressing if membrane staining is observed in ≥ 1% tumor cells among a minimum of 100 evaluable tumor cells.

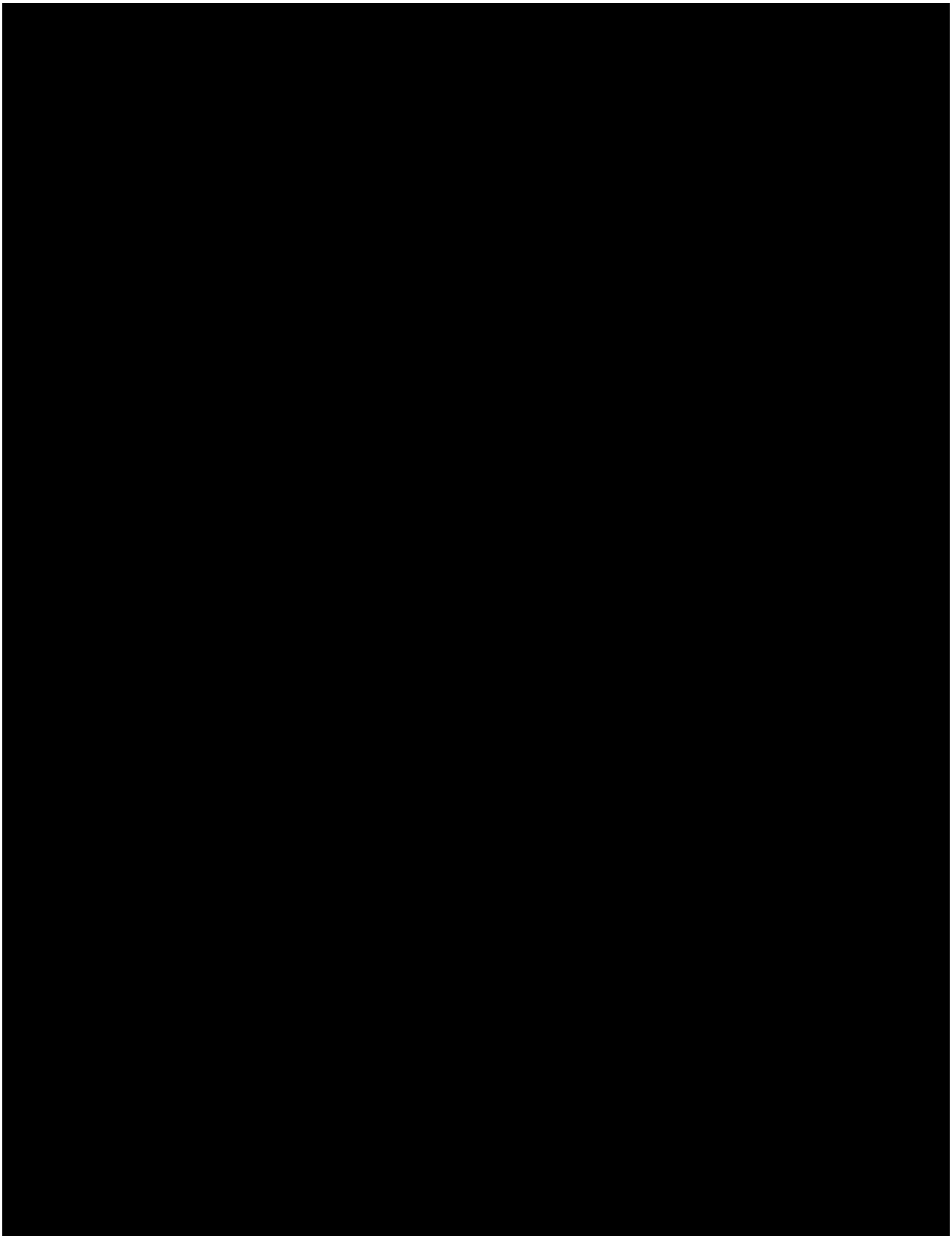
[redacted]

9.8.1.2 Cohort C

Archival FFPE tumor tissue collected within 3 months or fresh tissue for sectioned slides must be submitted for TMB testing. Ten unstained tumor tissue sections are required for TMB testing by Foundation Medicine unless TMB previous results from Foundation Medicine are available. PD-L1 testing is required unless results available from another BMS study, or a commercially available complementary diagnostic using an acceptable antibody (ie, 28-8, 22-C3, SP263). PD-L1 results obtained using antibody SP142 are not acceptable. Cohort C tissue will be assessed for biomarkers, as other cohorts.

[redacted]





9.9 Healthcare Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters will not be evaluated in this study.

9.10 Patient Reported Outcomes

In this study, patient-reported outcomes (PRO) will be measured using the Functional Assessment of Cancer Therapy-Lung (FACT-L) Version 4, a quality of life questionnaire to assess various functional dimensions and includes the Lung Cancer Subscale (LCS) that specifically assesses the treatment impact on lung cancer-related symptoms. The FACT-L is provided in Appendix 8.

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

In this study, approximately 400 participants will be treated in Cohort A and 400 participants will be treated in Cohort B.

In general, for nivolumab combined with ipilimumab, the safety profile to date is similar across tumor types, while select treatment related AEs of high grade (Grade 3-4) are rather uncommon. Their incidence per category was ≤ 5% in the CA209012 trial that tested nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks.[13]

An additional special population NSCLC cohort (Cohort A1) will include approximately 200 treated participants with one or more of the following criteria: ECOG PS 2, or PS ≤ 1

asymptomatic untreated brain metastases, renal or hepatic dysfunction, and/or HIV. Descriptive safety and efficacy analysis based on this cohort (Cohort A1) will be performed. [redacted]

[redacted]

Approximately 300 participants will be screened for TMB to achieve approximately 100 treated participants in Cohort C. [redacted]

[redacted]

10.2 Populations for Analyses

Population	Description
Enrolled	All participants who signed informed consent and were registered in IVRS
Treated	All participants who take at least 1 dose of any study medication.
Primary NSCLC cohorts treated participants	All treated participants in Cohort A and B. This is the primary cohort for safety and efficacy analyses
Special population NSCLC	All treated participants in the special population cohort (A1).

Population	Description
cohort treated participants	Exploratory analysis will be conducted by special populations.
PK	All treated participants with available serum time-concentration data.
Immunogenicity	All treated participants with available immunogenicity data.

10.3 Statistical Analyses

10.3.1 Efficacy Analyses

The primary efficacy analysis is scheduled to occur once all patients have initiated study therapy and have been followed for at least 9 months.

Endpoint	Statistical Analysis Methods
Secondary in Cohorts A, B, and C	Objective Response Rate (ORR) defined as the number and percentage of participants with a best overall response (BOR) of confirmed complete response (CR) or partial response (PR). Best overall response (BOR) is defined as the best response designation, recorded between the date of first dose and the date of the initial objectively documented tumor progression per RECIST v1.1 or the date of subsequent therapy, whichever occurs first. For participants without documented progression or subsequent therapy, all available response designations will contribute to the BOR determination. The ORR will be summarized by binomial response rates and their corresponding two-sided 95% exact CIs using the Clopper-Pearson method.
Secondary in Cohorts A, B and C	Progression-free survival (PFS) is defined as the time from first dosing date to the date of the first documented tumor progression, as determined by investigators (per RECIST v1.1), or death due to any cause, whichever occurs first. Participants who die without a reported prior progression will be considered to have progressed on the date of their death. Participants who did not progress or die will be censored on the date of their last evaluable tumor assessment. Participants who did not have any on study tumor assessments and did not die will be censored on the first dosing date. Participants who started any palliative local therapy or subsequent anti-cancer therapy without a prior reported progression will be censored on the date of their last evaluable tumor assessment prior to the initiation of the palliative local therapy or subsequent anti-cancer therapy, whichever procedure occurred first. OS is defined as the time from first dosing date to the date of death. A participant who has not died will be censored at last known date alive. OS and PFS will be summarized by Kaplan-Meier (KM) product-limit method for all treated participants. Median values of OS and PFS, along with two-sided 95% CI using Brookmeyer and Crowley method, will be calculated. Survival

Endpoint	Statistical Analysis Methods
	rates at fixed timepoints (eg, at 6 months) will also be estimated using KM estimates on the OS curve for all treated participants. Associated two-sided 95% CIs will be calculated using the Greenwood formula. Duration of objective response (DOR) is defined as the time between the date of first confirmed response to the date of the first documented tumor progression (per RECIST 1.1), or death due to any cause, whichever occurs first. Participants who neither progress nor die will be censored on the date of their last evaluable tumor assessment. Participants who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last evaluable tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy. DOR will be evaluated for responders (ie, participants with confirmed CR or PR) only.
Exploratory	Will be described in the statistical analysis plan finalized before database lock

10.3.2 Safety Analyses

The primary safety analysis is scheduled to occur once all patients have initiated study therapy and have been followed for at least 3 months.

Endpoint	Statistical Analysis Methods
Primary in Cohorts A, B, and C	The number and percentage of participants who experience high grade (Grade 3-4 and Grade 5) treatment related select and immune-mediated adverse events (imAEs) will be summarized for all treated participants. High grade (Grade 3-4 and Grade 5) treatment related select AEs and imAEs will be tabulated using worst grade per NCI CTCAE v4 criteria by system organ class and Medical Dictionary for Regulatory Affairs (MedDRA) preferred term. The analysis is scheduled to occur once all patients have initiated study therapy and have been followed for at least 3 months. The (select AEs consist of a list of preferred terms grouped by specific category (eg, pulmonary events, gastrointestinal events categories, etc). AEs that may differ from or be more severe than AEs caused by non-immunotherapies and AEs whose early recognition and management may mitigate severe toxicity are included as select AEs. The select AEs and the categories are defined by the Sponsor and the list that is the most current at the time of analysis will be used. Changes may be made to this list with each new version of MedDRA prior to database lock. Only select AEs occurring within 30 days of the last dose are included in the analysis. Immune-mediated AEs are specific events (or groups of preferred terms [PTs] describing specific events) that include pneumonitis, diarrhea/colitis, hepatitis,

Endpoint	Statistical Analysis Methods
	nephritis/renal dysfunction, rash, and endocrine (adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis). IMAE analyses included events, regardless of causality, occurring within 100 days of the last dose. These analyses will be limited to participants who received immunosuppressive medication for treatment of the event, with the exception of endocrine events (hypothyroidism/thyroiditis, hyperthyroidism, hypophysitis, diabetes mellitus, adrenal insufficiency), which were included in the analysis regardless of treatment since these events are often managed without immunosuppression.
Exploratory	Will be described in the statistical analysis plan finalized before database lock

10.3.3 Other Analyses

10.3.3.1 Patient Reported Outcomes

The analysis of FACT-L will be performed in all treated participants who have an assessment at screening/baseline and at least 1 follow-up assessment. The questionnaire completion rate for the FACT-L, defined as the proportion of questionnaires received out of the expected number (ie, the number of participants still on treatment in follow-up), will be calculated and summarized at each assessment point.

The FACT-L, including its subscales (LCS and TOI), will be scored using a 5-point scale (0 = not at all; 1 = a little bit, 2 = somewhat; 3 = quite a bit; 4 = very much). The ranges of possible total scores are 0 - 136 for the FACT-L, 0 - 28 for the LCS and 0 - 84 for the TOI, with a higher score representing better quality of life, improved symptomatology and enhanced physical/ functional outcomes, respectively. According to Functional Assessment of Chronic Illness Therapy (FACIT) scoring guidelines, in the event of missing responses for some of the questions/items, scores will be prorated using the average of the other answers in that scale. Additional details around the analyses will be provided in the statistical analysis plan.

The overall FACT-L (including the LCS and TOI) will be analyzed using descriptive statistics at each of the assessment time points. Summary statistics including the reporting of means, medians, ranges and standard deviation. Additional detail on methodology and analyses for the PRO secondary endpoint will be described in the statistical analysis plan.

10.3.3.2 Pharmacokinetic Analyses

The nivolumab and ipilimumab concentration data obtained in this study may be combined with data from other studies in the clinical development program to develop or refine a population PK model. This model may be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of nivolumab and to determine measures of individual exposure (such as steady-state peak, trough, and time-averaged concentration). In addition, model determined exposures may be used

for exposure-response analyses. Results of population PK and exposure response-analyses will be reported separately.

Immunogenicity, pharmacodynamic, [redacted] exploratory analyses will be described in the statistical analysis plan finalized before database lock.

10.3.4 Interim Analyses

There will be no formal interim analyses. Administrative interim analyses based on one single cohort or multiple cohorts may be performed at several times prior to completion of the study in order to support presentations or publications.

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
ACTH	adrenocorticotropic hormone deficiency
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
APC	antigen presenting cell
AST	aspartate aminotransferase
AT	aminotransaminases
BMS	Bristol-Myers Squibb
BOR	best overall response
BP	blood pressure
BSC	best supportive care
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CMV	cytomegalovirus
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CrCl	creatinine clearance
CRF	case report form, paper or electronic
CSR	clinical study report
CT	computed tomography
CTCAE	common terminology criteria for adverse events
CTLA-4	cytotoxic T lymphocyte-associated antigen 4
DILI	drug induced liver injury
DMC	data monitoring committee
[redacted]	
DOR	duration of response
EBUS	endobronchial ultrasound
EC50	median effective concentration
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
ELISA	Enzyme-Linked Immunosorbent Assay
EU	European Union
FACIT	Functional Assessment of Chronic Illness Therapy

Term	Definition
FACT-L	Functional Assessment of Cancer Therapy - Lung
FFPE	formalin-fixed paraffin-embedded
[redacted]	
FDA	Food and Drug Administration
[redacted]	
Hep B	hepatitis B
Hep C	hepatitis C
HBV sAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
HRQoL	Health Related Quality of Life
IASLC	International Association for the Study of Lung Cancer
IB	Investigator Brochure
IC50	50% inhibitory concentration
IEC	Independent Ethics Committee
IFN	interferon
Ig	immunoglobulin
IHC	immunohistochemical
IL	interleukin
imAE	immune-mediated adverse events
IMG	immunogenicity
IMP	investigational medicinal products
I-O	immuno-oncology
IP	investigational product
IRB	Institutional Review Board
IRT	interactive response technology
IV	intravenous
IVRS	interactive voice response system
KM	Kaplan Meier
LCS	Lung Cancer Subscale
LDH	lactate dehydrogenase
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	
MLR	mixed lymphocyte reaction
MM	medical monitor
MRI	magnetic resonance imaging

Term	Definition
[redacted]	
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PO	per os (by mouth route of administration)
PPK	population pharmacokinetic
PR	partial response
PRO	patient reported outcomes
PS	performance status
PT	preferred term
q	every
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RNA-seq	ribonucleic acid sequencing
ROS-1	proto-oncogene tyrosine-protein kinase 1
[redacted]	
SAE	serious adverse event
SD	study director
[redacted]	
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBLB	transbronchial lung biopsy
TKI	tyrosine kinase inhibitors
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
WBC	white blood cell
WOCBP	women of childbearing potential

APPENDIX 2 STUDY GOVERANCE CONSIDERATIONS

The term 'Participant' is used in the protocol to refer to a person who has consented to participate in the clinical research study. The term 'Subject' used in the eCRF is intended to refer to a person (Participant) who has consented to participate in the clinical research study.

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

- Good Clinical Practice (GCP),
- as defined by the International Council on Harmonisation (ICH)
- in accordance with the ethical principles underlying European Union Directive 2001/20/EC
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- applicable local requirements.

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

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

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

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

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, participant recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if applicable, also by local health authority) except where necessary to eliminate an immediate hazard(s) to study subjects.

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

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

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

If an amendment substantially alters the study design or increases the potential risk to the participant: (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).

FINANCIAL DISCLOSURE

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

INFORMED CONSENT PROCESS

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 participant volunteers to participate.

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

Investigators must:

- Provide a copy of the consent form and written information about the study in the language in which the participant is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
- Allow time necessary for participant or participant's legally acceptable representative to inquire about the details of the study.
- Obtain an informed consent signed and personally dated by the participant or the participant'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 participant's legally acceptable representative or legal guardian, and the participant subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the participant.

Revise the informed consent whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant or the participant's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the participant'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 participant records.

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

SOURCE DOCUMENTS

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.

STUDY TREATMENT RECORDS

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

If	Then
Supplied by BMS (or its vendors):	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 participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • non-study disposition (eg, lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study drug integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy. These records should include:

If	Then
	• label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

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

CASE REPORT FORMS

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

For sites using the Sponsor or designee electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by Sponsor or designee.

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

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

The completed CRF, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a sub-investigator and who is delegated this task on the Delegation of Authority Form. Sub-investigators in Japan may not be delegated the CRF approval task. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet Sponsor or designee training requirements and must only access the BMS electronic data capture tool using the unique user

account provided by Sponsor or designee. User accounts are not to be shared or reassigned to other individuals

MONITORING

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

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable. Certain CRF pages and/or electronic files may serve as the source documents:

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

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

RECORDS RETENTION

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

BMS or designee will notify the investigator (or head of the study site in Japan) when the study records are no longer needed.

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

RETURN OF STUDY TREATMENT

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

If	Then
Study treatments supplied by BMS (including its vendors	Any unused study treatments supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

If	Then
	If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors) (examples include study treatments sourced from the sites stock or commercial supply, or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The following minimal standards must be met:

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

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

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

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:

- Participant recruitment (eg, among the top quartile of enrollers), and/or;
- Involvement in trial design

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

APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW UP AND REPORTING

ADVERSE EVENTS

Adverse Event Definition:
An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study treatment 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 treatment, whether or not considered related to the study treatment.
Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term
Events <u>NOT</u> Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

SERIOUS ADVERSE EVENTS

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the participant 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) NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies: • a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event) • elective surgery, planned prior to signing consent • admissions as per protocol for a planned medical/surgical procedure • routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy) • medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases • admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason) • admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)
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 participant or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 9.2.7 for the definition of potential DILI.)

Pregnancy and potential drug induced liver injury (DILI) must follow the same transmission timing and processes to BMS as used for SAEs (see section 9.2.5 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy should be reported as SAE (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

EVALUATING AES AND SAES

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

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 treatment 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.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study treatment, and pregnancies must be reported to BMS (or designee) immediately within 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form.
  - The required method for SAE data reporting is through the eCRF.
  - The paper SAE Report Form is only intended as a back-up option when the electronic data capture (EDC) system is unavailable/not functioning for transmission of the eCRF to BMS (or designee).
    - In this case, the paper form is transmitted via email or confirmed facsimile (fax) transmission
    - When paper forms are used, the original paper forms are to remain on site
- Pregnancies must be recorded on a paper Pregnancy Surveillance Form and transmitted via email or confirmed facsimile (fax) transmission

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

APPENDIX 4 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 2. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. [c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Unacceptable Methods of Contraception*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal Sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action • Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal (coitus interruptus). • Spermicide only • Lactation amenorrhea method (LAM)

*** 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

1) Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.5 and the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting

APPENDIX 5 ECOG PERFORMANCE STATUS

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

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

APPENDIX 6 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS GUIDELINES (VERSION 1.1) WITH BMS MODIFICATIONS

1 EVALUATION OF LESIONS

Solid tumors will be evaluated using Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1) guideline with BMS modifications.[1]

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

1.1 Measurable

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

10 mm by CT/MRI scan (scan slice thickness no greater than 5 mm), or ≥2x slice thickness if greater than 5mm.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT/MRI scan (scan slice thickness recommended to be no greater than 5 mm).

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT/MRI scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

Note: Lesions on X-Ray are not to be selected as Target or Non-Target Lesions.

1.2 Non-Measurable

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

Note: Lesions on X-Ray are not to be selected as Target or Non-Target Lesions.

1.3 Special considerations regarding lesion measurability

1.3.1 Bone lesions

- Bone scan, PET scan and 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.

1.4 Baseline Documentation Of 'Target' And 'Non-Target' Lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Note: A maximum of two lesions can be selected per organ system. For example, a maximum of two lung lesions can be selected (selected from one lung or one lesion from each). A maximum of two lymph nodes can be selected at baseline, as the lymphatic system is considered one organ.

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

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple 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').

2 RESPONSE CRITERIA

2.1 Evaluation of Target Lesions

- **Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- **Partial Response (PR):** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD):** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
- **Not Evaluable (NE):** If one or more target lesions cannot be measured or adequately assessed as either fully resolved or too small to measure (due to missing or poor quality images), and the sum of diameters of the remaining measured target lesions (if any) has not increased sufficiently to meet Progressive Disease as defined above.

2.1.1 Special Notes on the Assessment of Target Lesions

2.1.1.1 Lymph nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

2.1.1.2 Target lesions that become 'too small to measure'

While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned as the reference diameter. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too

small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

2.1.1.3 Lesions that split or coalesce on treatment

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

2.2 Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- **Complete Response (CR):** Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10mm short axis).
- **Non-CR/Non-PD:** Persistence of one or more non-target lesion(s)
- **Progressive Disease (PD):** Unequivocal progression of existing non-target lesions.

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

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

2.2.1.1 When the patient also has measurable disease

In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. Pleural effusions, pericardial effusions and ascites will not be followed as target or non-target lesions and will not contribute to response or progression. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

2.2.1.2 When the patient has only non-measurable disease

This circumstance arises in some trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable

disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include, an increase in lymphangitic disease from localized to widespread, or may be described as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

2.2.2 New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

NOTE: Fluid collections (pleural effusions, pericardial effusions, and ascites) will not be considered new lesions and will not contribute to response or progression. In the event a new fluid collection is seen on a post-baseline imaging exam, a comment may be made, but the appearance of a new fluid collection alone should not result in an assessment of Progressive Disease (PD). A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline. A lesion identified on Chest X-Ray that was not present in prior CT can be considered a new lesion and will result in Progressive Disease (PD).

If a new lesion is equivocal, for example because of its small size, continued follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

2. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

2.3 Response Assessment

2.3.1 Evaluation of Best Overall Response

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

2.3.2 Time Point Response

At each protocol specified time point, a response assessment occurs. Table 2.3.2-1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore non-target) disease only, Table 2.3.2-2 is to be used.

Table 2.3.2-1: Time Point Response: Patients With Target (± Non-Target) Disease

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

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

Table 2.3.2-2: Time Point Response: Patients with Non-target Disease Only		
Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR = complete response, PD = progressive disease and NE = inevaluable		

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

2.3.3 Best Overall Response

Best response determination of complete or partial response requires confirmation: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point of ≥ 4 weeks (28 days) later. In this circumstance, the best overall response can be interpreted as in Table 2.3.3-1. When SD is believed to be best response, it must meet the protocol specified minimum time from the date of first treatment or randomization date.

For example, if the first scheduled follow-up imaging visit is Week 6 (± 7 days) for a particular protocol, a Best Response of SD can only be made after the subject is on-study for a minimum of 6 weeks (42 days) minus 7 days, for an absolute minimum time on-study of 35 days from the reference start date (reference date is considered Day 1 on study). If the subject is not on-study for at least this amount of time, any tumor assessment indicating stable disease before this time period will have a Best Response of NE unless PD is identified.

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

Table 2.3.3-1: Best Overall Response (Confirmation of CR and PR Required)		
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**Best Overall Response**
CR	CR	CR
CR	PR	SD, PD OR PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD

Table 2.3.3-1: Best Overall Response (Confirmation of CR and PR Required)		
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**Best Overall Response**
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.

2.3.4 Confirmation Scans

Verification of Response: To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive or subsequent repeat assessments that should be performed no less than 28 days after the criteria for response are first met. Subsequent documentation of a CR may provide confirmation of a previously identified CR even with an intervening NE or PR (eg, CR NE CR or CR PR CR). Subsequent documentation of a PR may provide confirmation of a previously identified PR even with an intervening NE or SD (eg, PR NE PR or PR SD PR). However, only one (1) intervening time point will be allowed between PR/CRs for confirmation.

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

REFERENCES

[1] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228-47.

APPENDIX 7 COUNTRY SPECIFIC AMENDMENTS

Germany HIV Testing requirement:

This amendment responds to the German Health Authority's (PEI) request to:

- Change eligibility to ensure that HIV positive participants are excluded from the study
- Add HIV testing to screening laboratory tests for participants enrolled in Germany.

This amendment will be implemented at sites after IRB approval. These revisions apply to all participants in the future who enroll on the study, and where applicable, to all participants currently enrolled.

Changes to the Protocol:

Page	Protocol Section	Revised Protocol Text
Page 12	Table 2-1 Screening Procedural Outline (CA2099LA)	Add "HIV testing" to list of laboratory tests.
Page 43	Section 6.2 Exclusion Criteria, 1) Medical Conditions j)	Replace "Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). Testing for HIV must be performed at sites mandated by local requirements" with "Positive test for HIV"
Page 78	Section 9.4.3 Clinical Safety Laboratory Assessments	Replace "HIV testing (if mandated locally)" with "HIV testing".

APPENDIX 8 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.

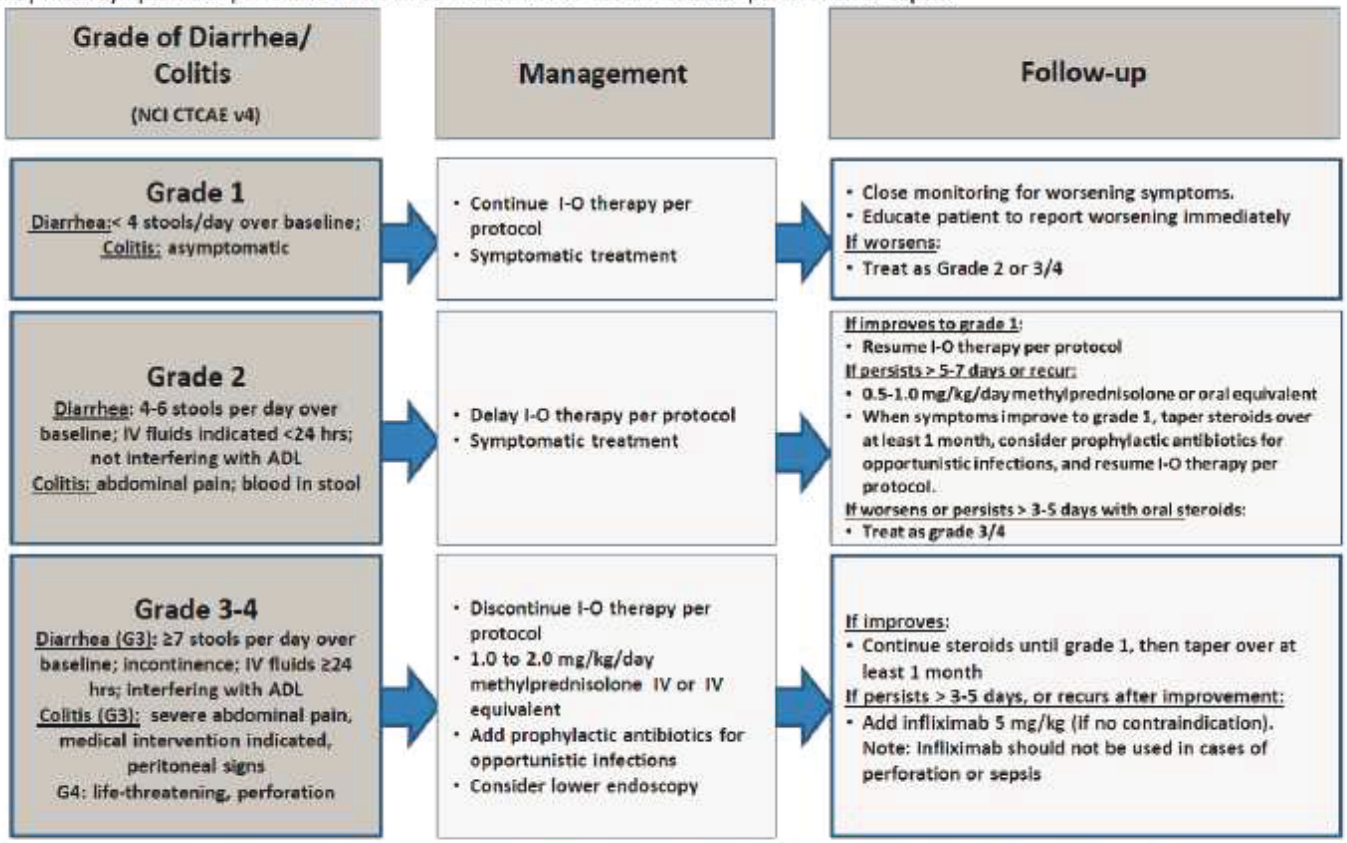
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

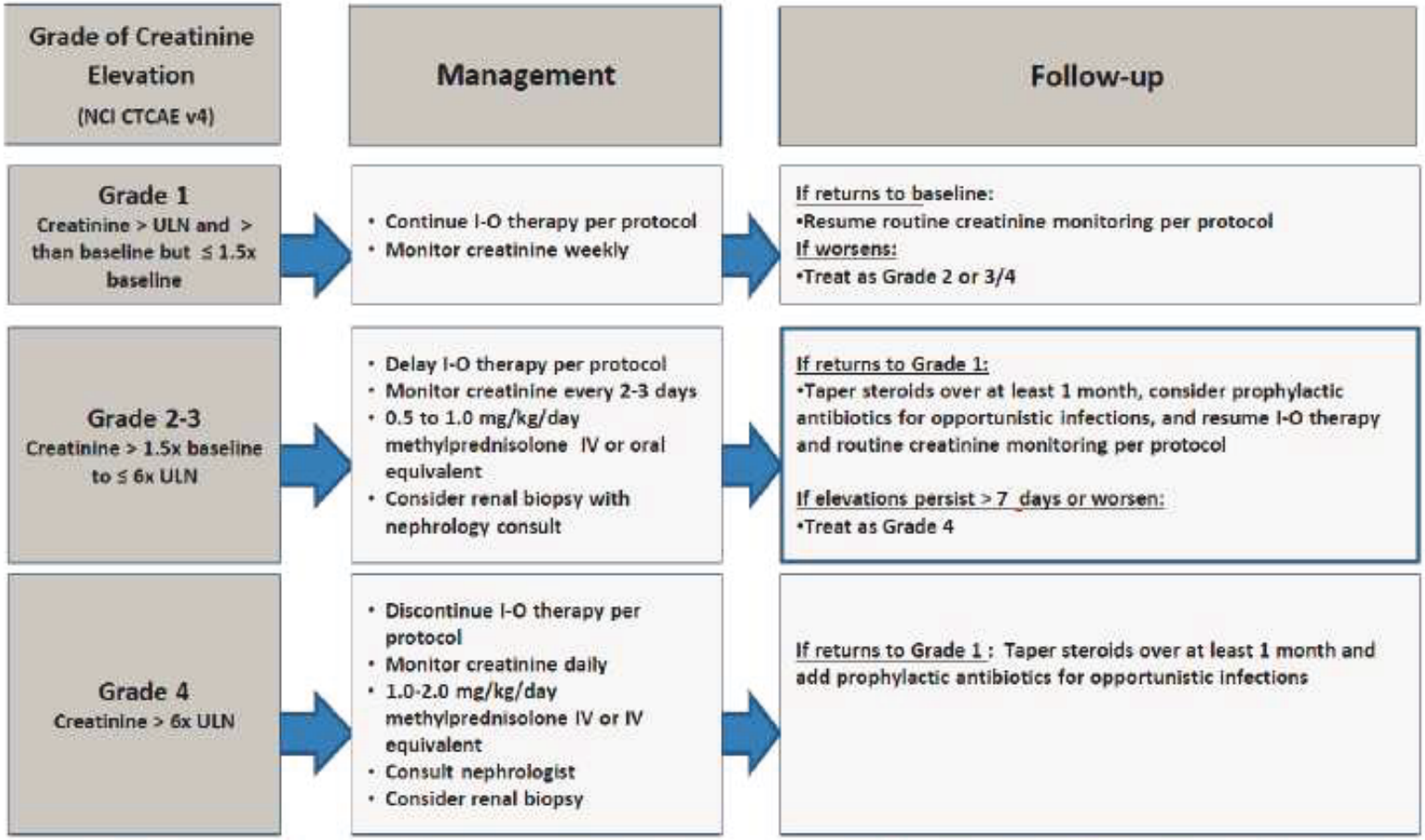


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2018

Renal Adverse Event Management Algorithm

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

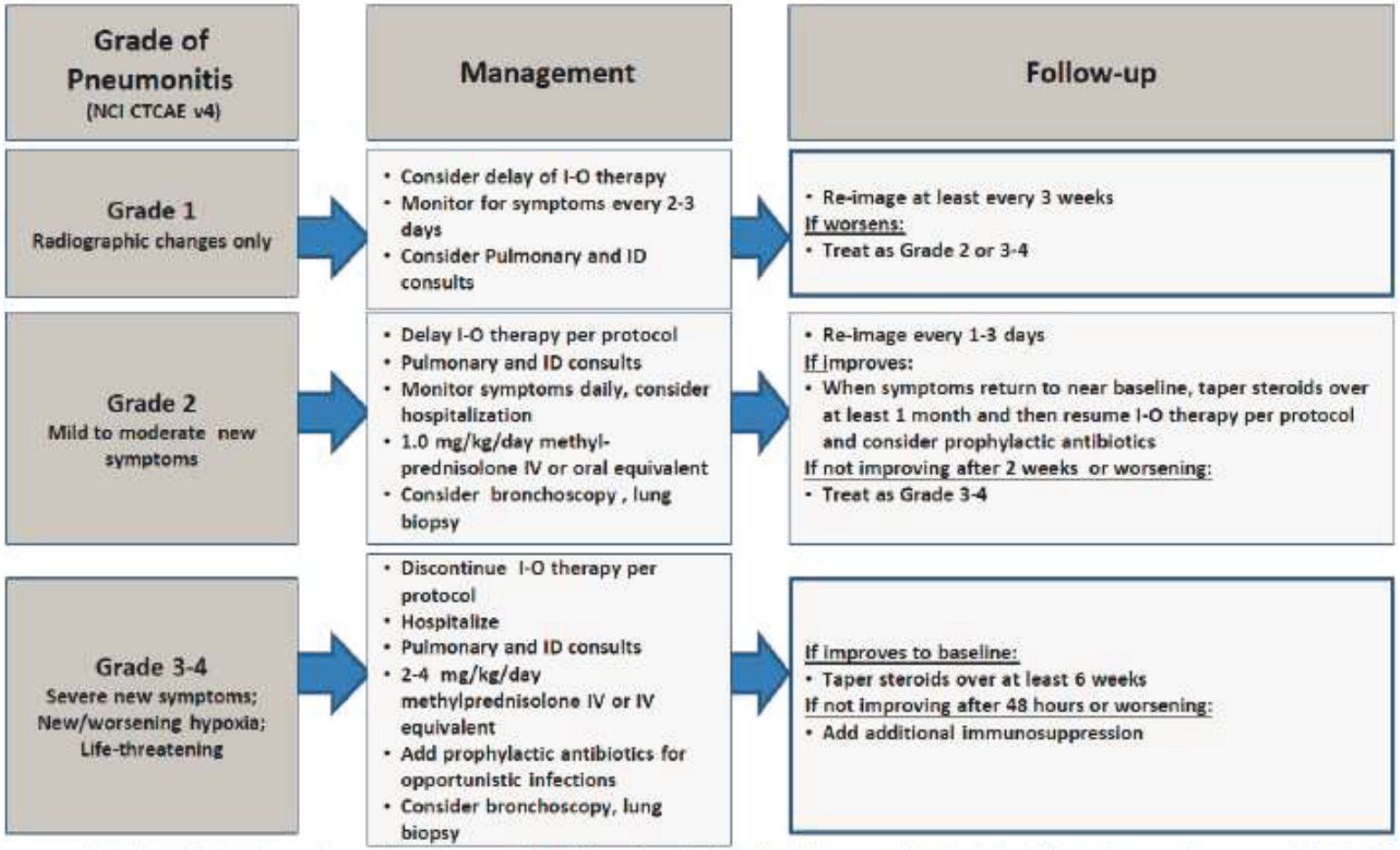


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2018

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

27-Jun-2018

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.

Grade of Liver Test Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 AST or ALT > ULN to 3.0 x ULN and/or T. bili > ULN to 1.5 x ULN	• Continue I-O therapy per protocol	• Continue LFT monitoring per protocol If worsens: • Treat as Grade 2 or 3-4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or T. bili > 1.5 to ≤ 3 x ULN	• Delay I-O therapy per protocol • Increase frequency of monitoring to every 3 days	If returns to baseline: •Resume routine monitoring, resume I-O therapy per protocol If elevations persist > 5-7 days or worsen : • 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
Grade 3-4 AST or ALT > 5 x ULN or T.bili >3 x ULN	• Discontinue I-O therapy* • Increase frequency of monitoring to every 1-2 days • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent* • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist	If returns to grade 2: • Taper steroids over at least 1 month If does not improve in >3-5 days, worsens or rebounds: • Add mycophenolate mofetil 1 g BID • If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines

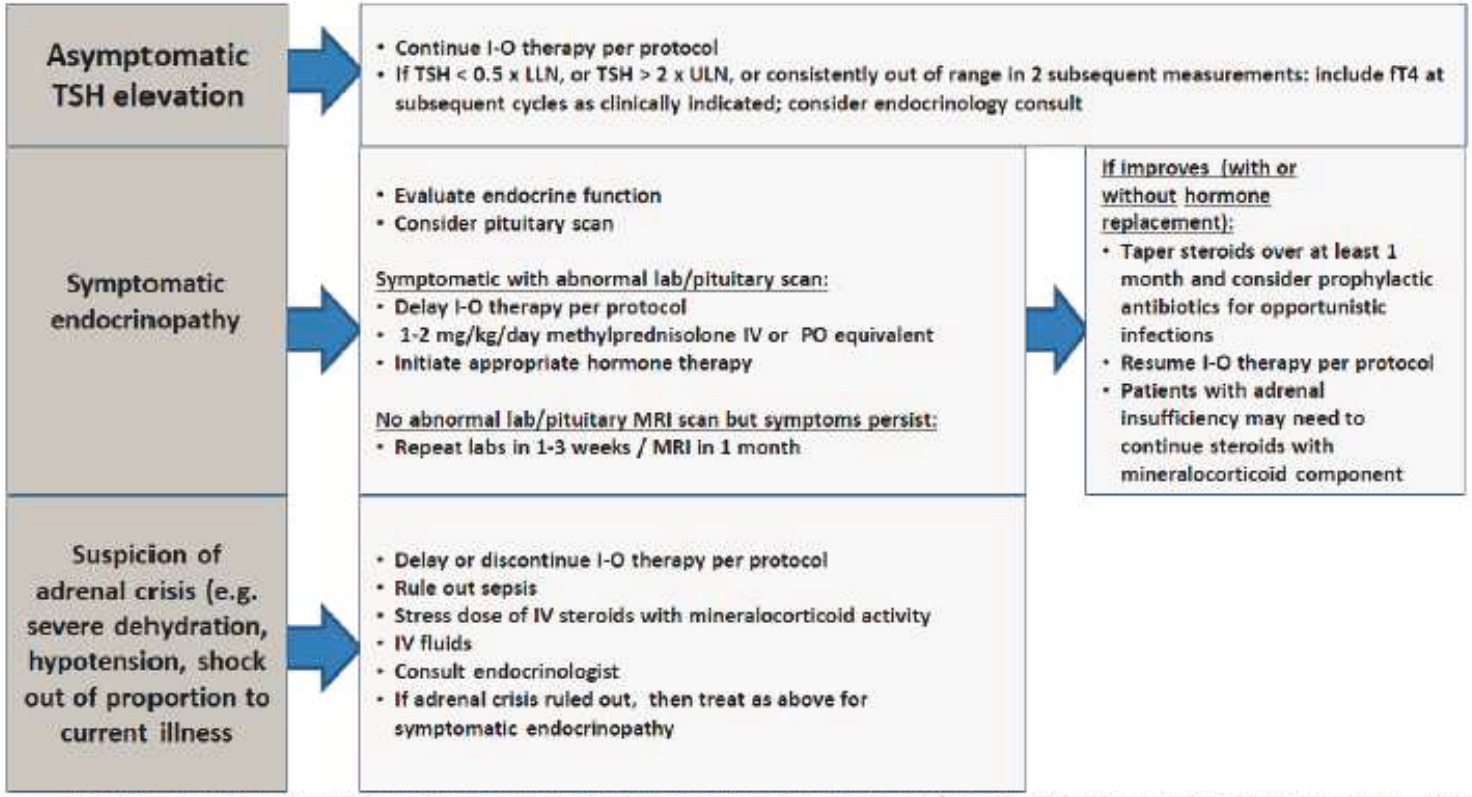
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

27-Jun-2018

Endocrinopathy Adverse Event Management Algorithm

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

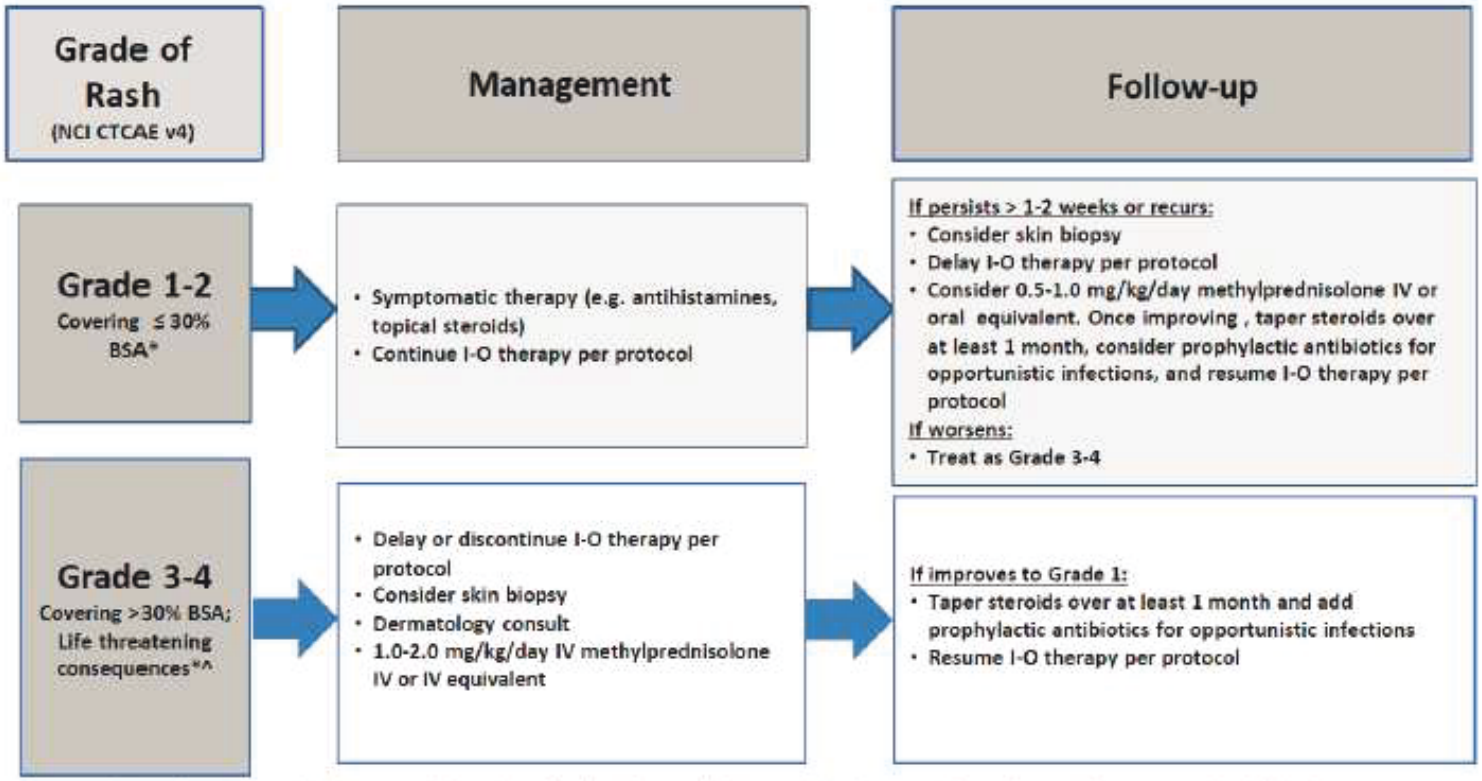


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2018

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.

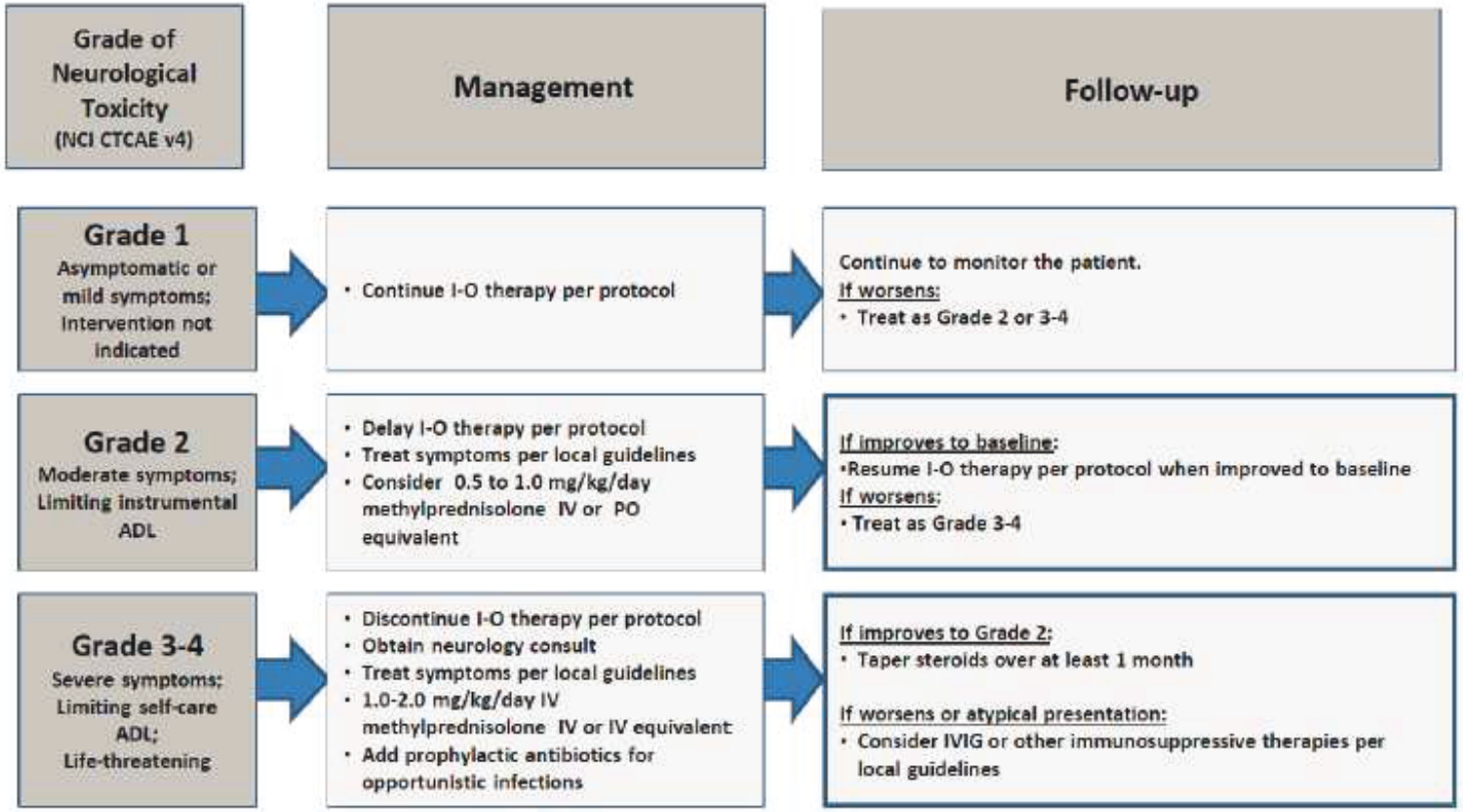
*Refer to NCI CTCAE v4 for term-specific grading criteria.

^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.

27-Jun-2018

Neurological Adverse Event Management Algorithm

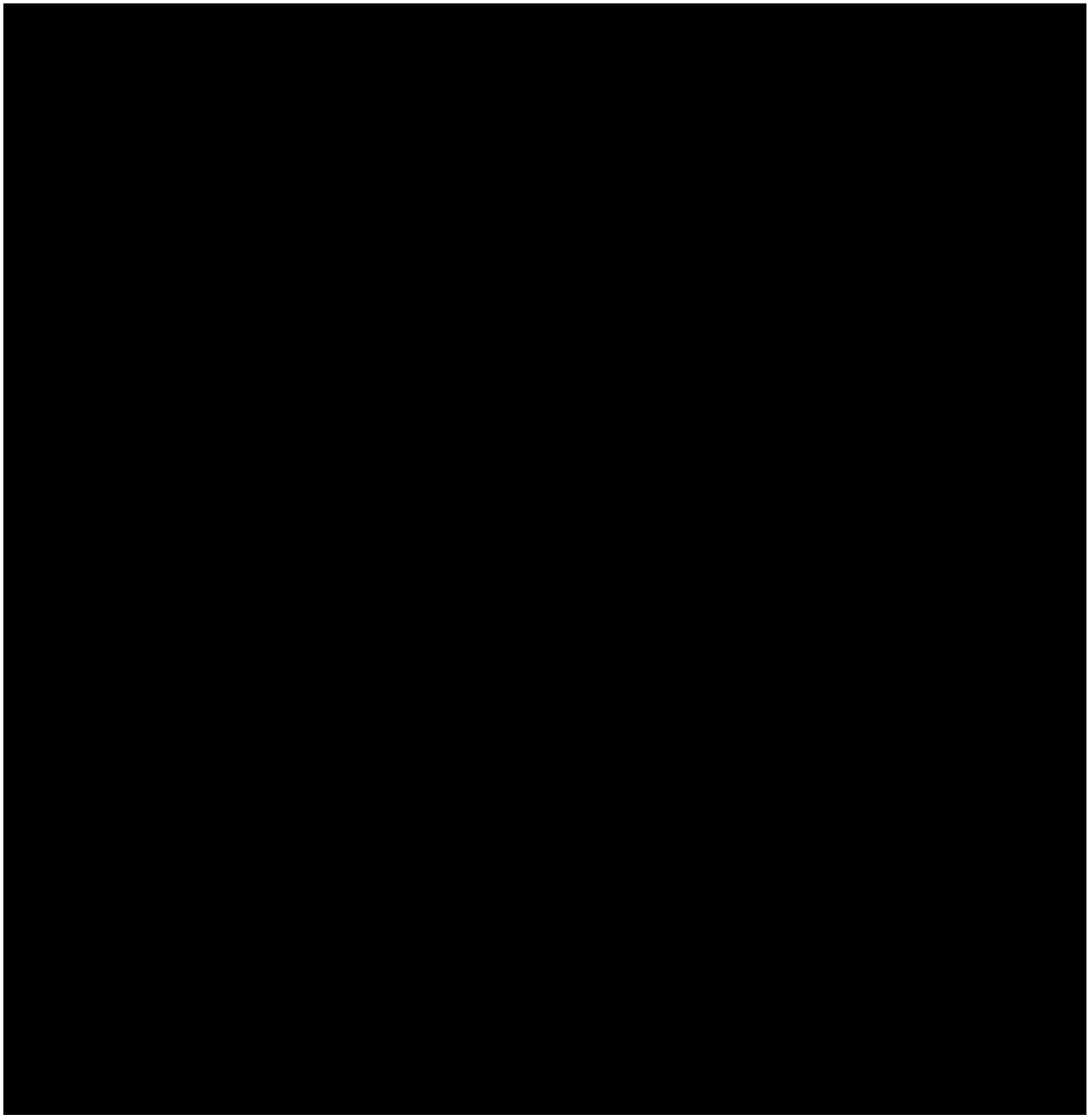
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

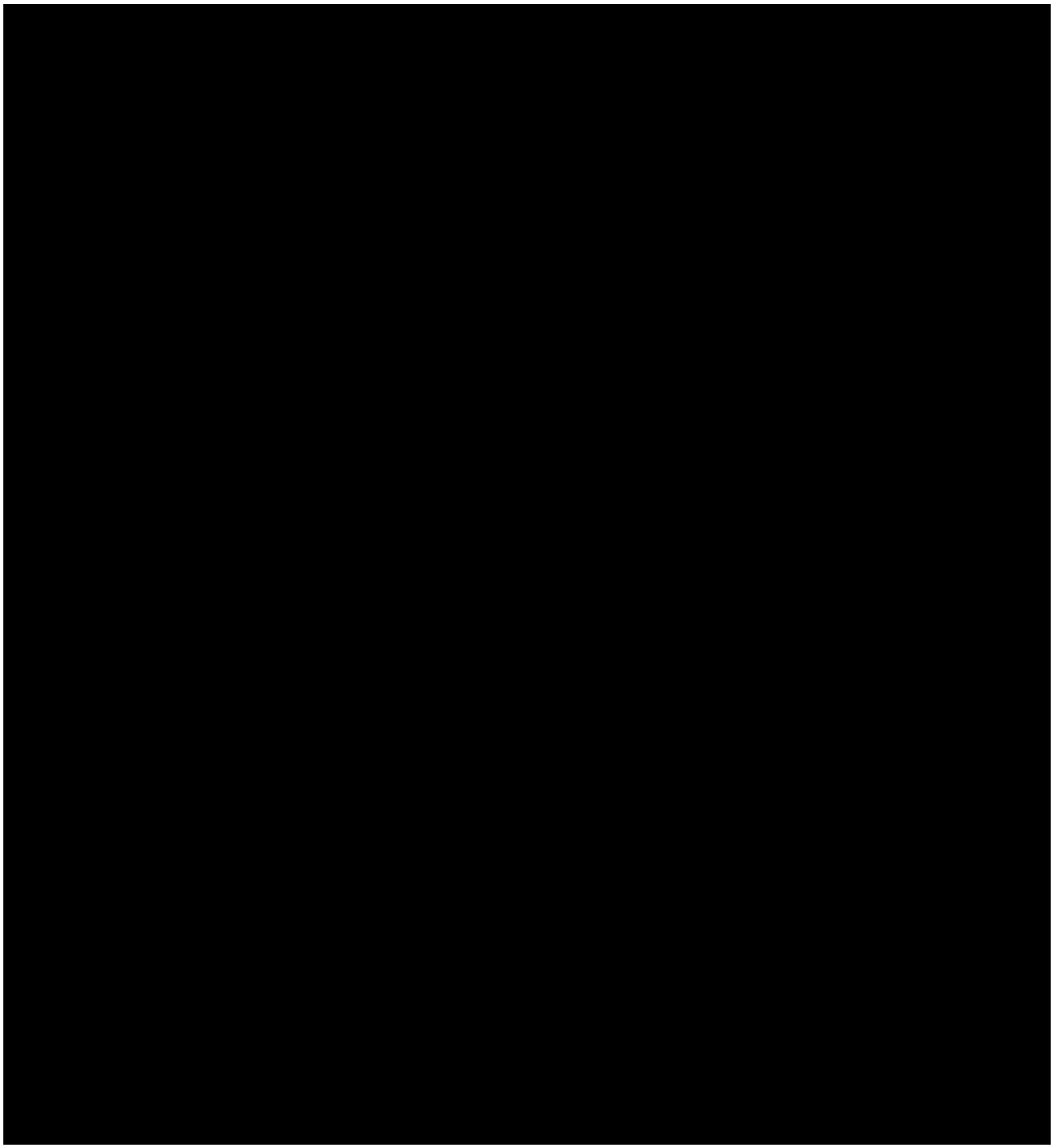


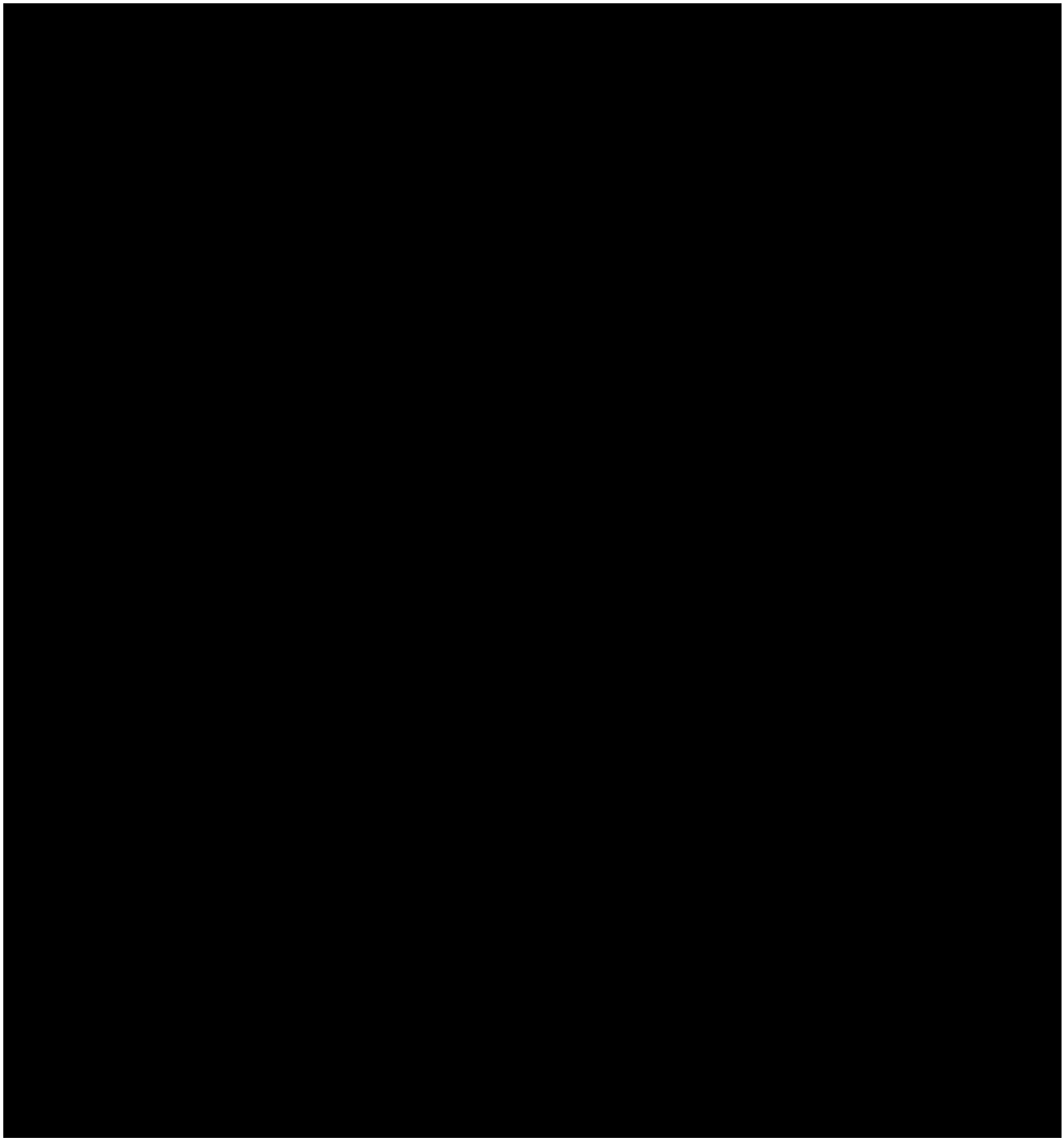
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2018

APPENDIX 9 FACT-L







APPENDIX 10 COUNTRY SPECIFIC AMENDMENT

This amendment is being produced in response to a request from the German Health Authority (PEI).

- Adjust the exclusion criteria to ensure that HIV positive participants are excluded from the study.
- Added "HIV" test to Laboratory Tests as screening for participants enrolled in Germany.

Timing: This amendment is to be implemented only after IRB approval at each site.

Scope: Revisions apply to future participants enrolled on the study, and where applicable, to all participants currently enrolled.

Criteria for exclusion of HIV-positive Participants in Germany

	Country-specific language
Section 2 Flow Chart/Time and Events Schedule, Table 2-1: Screening Assessments-Laboratory Tests	Add "HIV" to the list of laboratory tests
Section 6.2 Exclusion Criteria, Exclusion criterion 2h	"Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)"to be replaced with "Positive test for HIV".
Section 9.4 Safety Assessments (baseline laboratory assessments)	Add "HIV" test to baseline local laboratory assessments to be done within 14 days prior to first dose.

APPENDIX 11 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for the Revised Protocol 05, 04-Jun-2018

The study protocol has been updated to include safety as the primary endpoint for Cohort C aligning with the primary objective of the study. Additional changes updated document to align with current program standards.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Updated study personnel	To update study personnel
Section 1 Synopsis Table 4-1 Objectives and Endpoints Figure 5.1-1 CA209817 Study Design Schema Section 10.3.1 Efficacy Analyses and Section 10.3.2 Safety Analyses	Modified objectives and endpoints for Cohort C	To include safety as the primary endpoint for Cohort C
Section 1 Synopsis Figure 5.1-1 CA209817 Study Design Schema Section 5.2.1 All Cohorts (NSCLC) Section 10.1 Sample Size Determination [redacted]	Modified cohort size for Cohort C	To include safety as the primary endpoint for Cohort C
[redacted]		
Table 2-1 Screening Procedural Outline Section 6.2 Exclusion Criteria	Updated language for EGFR mutation and ALK testing requirements	To provide clarity for sites that test results from either local and/or central laboratories are acceptable
Table 2-1 Screening Procedural Outline Table 2-2 Treatment Phase Assessments	Updated radiographic assessments for brain metastases	To clarify inconsistency in the MRI requirements versus preferred modality for the brain scans
Section 5.5.5 Rationale for Tumor Mutation Burden Testing	Modified document with updated CA209227 study results	To update document with study results
Section 6.2 Exclusion Criteria 3)c Section 7.7.1 Prohibited and/or Restricted Treatments	Allowed marijuana use by prescription or by local legal status	Allowed marijuana use for treatment of cancer/cancer treatment symptoms
Section 7.1 Treatments Administered	Updated treatment procedures	To provide clarity on infusion steps

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.4.4 Management Algorithms for Immuno-Oncology Agents	Added monitoring for myotoxicity	[redacted]
Section 7.4.5.1 Criteria to Resume Treatment for Cohorts A, B, and C	Added language for study discontinuation for adrenal insufficiency	To align criteria with Investigator Brochure for safety
Section 8.1.1.1 Nivolumab Discontinuation for Cohorts A, B, and C	Updated language study discontinuation language	To align criteria with internal program standards for safety

Overall Rationale for the Revised Protocol 04, 25, Oct-2017

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis: Rationale	Added new study cohort (Cohort C) of first-line NSCLC participants with high tumor mutation burden (TMB).	High TMB cohort added to evaluate response to immuno-oncology (IO) therapy in this population.
Synopsis: Primary Objectives and Endpoints	Primary objective (objective response rate [ORR]) added for Cohort C	ORR is the endpoint for the additional Cohort C
Synopsis: Secondary Objectives	Modified secondary objective information for the assessment of progression-free survival (PFS), overall survival (OS), and duration of response (DOR) across other cohorts. Updated PRO assessments to include all patients. Characterized the safety assessments for nivolumab.	Updated secondary objectives and information to align with study design and statistical analyses.
Synopsis: Exploratory Objectives and Endpoints	Added information to assess the screen failure rate as an exploratory endpoint for Cohort C	The screen failure rate is an endpoint to evaluate prospective testing for the Cohort C high TMB population.
Synopsis: Overall Design	Updated the study design and schema to include cohort C Added the maximum treatment duration of 2 years	The description of study design includes the new study cohort C. The maximum treatment duration was added to align with current program characterization of nivolumab efficacy.
Synopsis: Number of Participants	Added anticipated participant numbers for Cohort C (screened, n = 1000 and enrolled n = 200)	Anticipated enrollment for high TMB population (Cohort C) added.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2 Table 2-1: Screening Procedure Outline	Added tissue requirements for biomarker assessments for Cohort C (15 slides for PD-L1 and TMB testing).	Information on biomarkers was added for Cohort C.
Section 2 Table 2-1: Screening Procedure Outline	Time window changed from ≤ 28 days to ≤ 42 days. FSH level was added to the screening visit.	The screening visit was expanded to allow for TMB testing. The FSH level was added to test under 55 years of age female participants as per Appendix 4.
Section 2 Table 2-2: Treatment Phase Assessments	Changed the cycle window to ±5 days.	The cycle window was increased from 3 to 5 days to allow sites to complete procedures with addition of Cohort C
Section 3 Introduction	Added TMB information and definition.	Introductory information added regarding the description and definition of the TMB
Section 3.1.2: NSCLC Background	Descriptive information added on the NSCLC prognosis and recent scientific information. Removed information regarding major AEs related to platinum doublet chemotherapy regimens. Removed other treatment options for non-squamous histology NSCLC.	Updated the background section with current NSCLC information. Section was updated for clarity.
Section 4 Table 4-1: Objectives and Endpoints	Updated primary, secondary, and exploratory objectives to match synopsis	ORR is the endpoint for the additional Cohort C Updated secondary objectives information to align with study design and statistical analyses Anticipated enrollment for high TMB population (Cohort C) added.
Section 5.1: Overall Design	Added Cohort C information and updated study schematic	Information on Cohort C was added to the overall design section.
Section 5.1.1: Dosing	Added the new Cohort information and the maximum treatment duration.	This section was updated to incorporate Cohort C. The maximum treatment duration was added to align with current program characterization of nivolumab efficacy.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.2.1: All Cohorts (NSCLC)	Added description of Cohort C, including the number of participants.	This section describes Cohort C and cohort size.
Section 5.3: End of Study Definition	Removed information regarding the primary analysis scheduling.	The timing of primary analysis is described in the statistical section and removed from end of study definitions.
Section 5.4: Scientific Rationale for Study Design	Added scientific rationale for inclusion of TMB assessments in Cohort C and Cohorts A, A1, and B. Added nivolumab monotherapy safety information for Cohort A1.	This section updated to include scientific rational information, historical rationale to be compliant with all new information.
Section 5.5.3: Rationale for Two Year Duration of Treatment	Updated maximum duration of 2 years of treatment and added scientific rationale.	The maximum treatment duration was added to align with current program characterization of nivolumab efficacy.
Section 5.5.4: Justification for Removing Retreatment	Language added to remove the retreatment option.	Discontinuation of retreatment was added to align with current program characterization of nivolumab efficacy.
Section 5.5.5: Rationale for Tumor Mutation Burden Testing	Added information and justification for TMB testing.	Added to provide clarity of TMB testing rationale.
Section 6.1: Inclusion Criteria	Added additional information to PD-L1 immunohistochemical (IHC) testing, and removed allowing use of previous PD-L1 IHC test.	Updated to conform to study specific requirements surrounding PD-L1.
Section 6.1: Inclusion Criteria	Added requirement about sufficient tissue requirements for Cohorts A, A1, (10-15 FFPE slides) and C (15 slides). Allows previous approved testing of TMB and PD-L1.	Updated tissue requirements to allow for clarity in biomarker requirements and testing in protocol.
Section 6.1: Inclusion Criteria	Added FSH testing to inclusion criteria	The FSH level was added to test under 55 years of age female participants as per Appendix 4.
Section 6.2: Exclusion Criteria	Exceptions to HIV exclusion were added for Cohort A1 participants.	This information was added for clarity in the special population.
Section 6.2: Exclusion Criteria	Added botanical preparations as an exclusion criterion within 2 weeks prior to randomization.	This exclusion criterion will limit potential effects of these concomitant treatments.
Section 6.2: Exclusion Criteria	Changed limits for Physical and Laboratory Test Findings for Cohorts A, B, and C.	Updated to comply with program requirements for drug safety.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.1.1: Cohort A, Cohort A1 (optional), and Cohort B	Updated the timing of treatment infusion for participants who require small volumes and treatment windows.	Updated for study specific requirements.
Section 7.4.1: Dose Delay Criteria	Updated the dose delay criteria for multiple items.	Updated per program specific requirements for drug safety..
Section 7.7.1: Prohibited and/or Restricted Treatments	Added information on botanical preparations	This restriction will limit potential effects of these concomitant treatments.
Section 7.7.2.1: Palliative Radiotherapy (All Cohorts)	Added information about palliative radiotherapy exclusion	Added to align with study design
Section 7.7.3: Permitted Therapy	Added information on corticosteroids as a permitted therapy.	Added to comply with program standards on corticosteroid therapy
Section 8.1.1.1: Nivolumab Dose Discontinuation for Cohorts A, B, and C	Added discontinuation information regarding Grade 3 nonskin, drug-related AEs lasting >7 days..	Added to comply with program specific standards for drug safety.
Section 9.8.1.1: Tumor Tissue Specimens	Updated tumor tissue requirements, timing, and PD-L1-specific language.	Updated tissue requirements to allow for clarity in biomarker requirements and testing in protocol.
Section 9.8.1.2: Cohort C	Added tissue requirements for Cohort C	Added to provide tissue information for Cohort C
[redacted]		
Section 10.1: Sample Size Determination	Added sample size information for Cohort C	Information needed for Cohort C
Section 10.3: Efficacy Analyses	Added statistical information for the updated primary and secondary objective	Complies with new statistical information for the updated primary and secondary objectives.
Section 10.3.4: Interim Analyses	Information added to allow for the administrative interim analyses	Added to comply with program specific standards.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 10: References	Added new references for the new information added to the protocol	New references added for new citations.
Appendix 10 Summary of Key Changes of Revised Protocol 04	Added Appendix 10 table	Incorporates previous Summary of Key Changes of Revised Protocol 04 keeping information in single document

OVERALL RATIONALE FOR THE REVISED PROTOCOL 03

[redacted] changes from protocol amendments and administrative letters were incorporated into a revised protocol.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Change in study personnel	Change in Medical Monitor as per Administrative Letter 03
Title Page	Change in title	Reflect secondary objectives and endpoints.
Synopsis; Secondary Objectives and Endpoints, Exploratory Objectives and Endpoints, Overall Design, Schema, Number of Participants, Study Treatment, Section 4.1 Overall Design, Section 4.2.1 NSCLC Cohorts, Section 4.1.2 DMC, Section 4.2 Number of participants, Section 4.4 Scientific Rationale for Study Design, Section 5.1.1 Inclusion Criteria For Cohort A1 Special Population, Section 5.2 Exclusion Criteria 4), Section 6.4.1.1 Dose Delay Criteria for Special Population (Cohort A1), Section 6.4.5.3 Criteria to Resume Nivolumab and Ipilimumab for Special Population (Cohort A1), Section 5.2 Exclusion Criteria 3b), Section 8.5.1 Pharmacokinetic And Immunogenicity Collection, Section 9.1 Sample Size Determination, Section 9.2 Population for Analyses,	Addition of special population (Cohort A1) and relevant language for data collection and analyses	Incorporation of additional language for special population (Cohort A1) from Site Specific Amendment 01
Table 2-2 On Study Assessments, Table 8.4.2-1 Clinical Safety Laboratory Assessments	Language creatinine clearance assessment updated for participants with renal clearance	Incorporation of additional language for participants with renal impairment from Site Specific Amendment 01
Section 5.2 Exclusion Criteria	Prior treatment with nivolumab or ipilimumab requires Medical Monitor permission	Incorporation of additional language for special population (Cohort A1) from Site Specific Amendment 01

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Schedule of Activities Table 2-1, Table 8.4.2-1 Laboratory Assessment Panels	Added HIV testing for participants in Germany.	Incorporation of additional language for HIV testing from Site Specific Amendment 02
[redacted]		
Section 5.5.3 Rationale for the Duration of Treatment with Nivolumab and Ipilimumab	Added immunotherapy treatment duration of 24 months.	Added standard program language
Section 7.7.2 Other Restrictions and Precautions	Allowed corticosteroid use was changed.	New language provides greater clarity.
Section 8.1.1.3 Nivolumab and Ipilimumab Dose Discontinuation for Special Population (Cohort A1)	Section added	Incorporation of additional language for special population (Cohort A1) from Site Specific Amendment 01