Official Title of Study:

An Open Label, Safety Study of Participants with Non-Small Cell Lung Cancer Receiving Second-Line Nivolumab Monotherapy in Asia
(CheckMate 870: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 870)

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Clinical Protocol CA209870

An Open Label, Safety Study of Participants with Non-Small Cell Lung Cancer Receiving Second-Line Nivolumab Monotherapy in Asia

(CheckMate 870: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 870)

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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 02	25-Oct-2017	Incorporates Amendment 02
Amendment 02	25-Oct-2017	Change the efficacy objective, endpoint, and analyses [redacted] to secondary classification.
Revised Protocol 01	20-Mar-2017	Incorporates Amendment 01
Amendment 01	20-Mar-2017	• Treatment duration will have a 2-year stopping rule • Number of EGFR mutation participants will be capped to 40 participants • PD-L1 testing [redacted] will be evaluated in a central laboratory.
Original Protocol	23-Nov-2016	Not Applicable

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1 SYNOPSIS

Protocol Title: An Open Label, Safety Study of Participants with Non-Small Cell Lung Cancer Receiving Second-Line Nivolumab Monotherapy in Asia

Study Phase: 3b

Rationale: Non-small cell lung cancer (NSCLC) second line (2L) will be launched in China in July, 2018 based on the results of the CA209-078 study, an open-label randomized multinational phase 3 trial of nivolumab versus docetaxel in previously treated participants with advanced or metastatic NSCLC. NSCLC 2L treatment in the study used weight-based dosing and will be the first indication for nivolumab in China. In CA209078 study weight based dosing with a 60 minutes infusion time was used. The study excluded patients with tumors harboring EGFR activating mutation or ALK rearrangement in order to control potential confounding OS outcomes due to subsequent use of new generation TKI. Additionally, the study used conventional eligibility criteria for phase 3 trials and limited enrollment of patients such as those with HBV infection, which is more frequently found in clinical practice in Asia. However, modeling and simulation, as well as preliminary PK data support the use of flat dose as well and a shorter 30 minute infusion time in this study. As flat based dosing will be the future nivolumab dosing for NSCLC patients and a 30 minute infusion time is more convenient for participants, this study will gather safety and efficacy data on these subjects.

With the NSCLC 2L indication for nivolumab, important clinical practice questions and regulatory issues remain to be answered.

1) **EGFR-mutation and ALK translocation subset data gap:** A data gap exists in patients in China regarding EGFR mutation and ALK translocation patients, as they were excluded in CA209-078 study
2) **HBV-infection subset data gap**: CA209-078 study excludes participants with positive results of hepatitis B virus surface antigen (HBV sAg). The HBV prevelence is 7.18% among Chinese population from 1 to 59 years old based on the natioanl epidemiological serosurvey of hepatitis B in China in 2006. Recent data from Shanghai Chest Hospital shows that approximately 15% of lung cancer patients are HBV sAg positive, indicating a huge data gap in these patients.
3) **Benefit of shorter infusion time benefit gap**: The risk/benefit profile for nivolumab has been characterized primarily using a 60 minute infusion. Longer infusion times place an additional burden on patients and treatment cnistered using shorter infusion times will diminish some of this burden.
4) **Flat Dose**: Nivolumab 240mg every 2 weeks flat dose will be more convinient than 3mg/kg every 2 weeks (weight-based dosing) in clinical practice. Evaluating the flat fose will demonstrate that nivolumab can be safely administered using flat dose and will diminish some of this burden of weight-based dosing.
5) [redacted] **Patient Reported Outcomes (PRO) data gap:** Nivolumab will be the first approved immunoncology drug in China and no comprehensive data set exists on patient reported outcomes (PROs) [redacted] data from patients diagnosed with NSCLC. PRO [redacted] data are needed demonstrate the

high-value of these innovative drugs and to support policy decision making. This study will collect a robust data set for broader patient population, as compared to study CA209078. Notably, this study will collect data on patients who are EGFR or ALK positive and HBV infected. Additionally, this study will evaluate shorter infusion times and impact on quality of life and is of interest.

6) **Future Post-Approval Committment**: The China Food and Drug Administration (CFDA) strongly indicated that of a future requirement of PAC (post-approval-commitment) study to collect nivolumab safety data in Chinese cohort. Thus, team proposes to author the Chinese cohort safety study in advance of successful global launch.

Study Population: This open label, phase 3b trial will include participants with advanced or metastatic NSCLC.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate safety and tolerability in non-HBV infected participants with advanced or metastatic NSCLC who have progressed during or after one prior systemic therapy and are treated with nivolumab monotherapy with an infusion duration of 30 min	• Incidence and severity of high grade (combined CTCAE v4 Grade 3-4 and Grade 5) treatment-related select adverse events in non-HBV infected participants.
Secondary	
• To assess safety and tolerability in HBV infected participants with advanced or metastatic NSCLC who have progressed during or after one prior systemic therapy and are treated with nivolumab monotherapy with an infusion duration of 30 min	• Incidence and severity of all high grade (combined CTCAE v4 Grade 3-4 and Grade 5) treatment-related select adverse events in HBV participants
• To assess safety and tolerability in all participants	• Incidence and severity of AEs and specific laboratory abnormalities in all treated subjects
• To evaluate efficacy in participants with advanced or metastatic NSCLC who have progressed during or after one prior systemic therapy and are treated with nivolumab monotherapy	• Collection of overall survival (OS), time to treatment failure (TTF), progression free survival (PFS), objective response rate (ORR) , duration of tumor response (DOR) by tumor histology (SQ or NSQ), tumor PD-L1 expression level (PD-L1 negative or PD-L1 positive), by infection status (HBV infection or non-HBV infection), and by molecular type (EGFR mutation, ALK translocation, or WT).
• **Exploratory**	

Objectives	Endpoints
• To assess overall health status and health utility	• The 3-level version of the EQ-5D (EQ-5D-3L) visual analog scale (VAS) and utility index, respectively
• To evaluate the proportion of participants exhibiting disease-related symptom deterioration at week 12 and by week 24	• Lung Cancer Symptoms Scale (LCSS) will use disease-related symptom deterioration rate at week 12 and week 24 and is defined as the proportion of treated subjects who had 10 points or more increase from baseline in Average Symptom Burden Index (ASBI) score at any time between first dosing and at week 12 and week 24.
[redacted]	

Overall Design: This single arm, open label, phase 3b clinical trial will enroll participants with advanced or metastatic NSCLC.

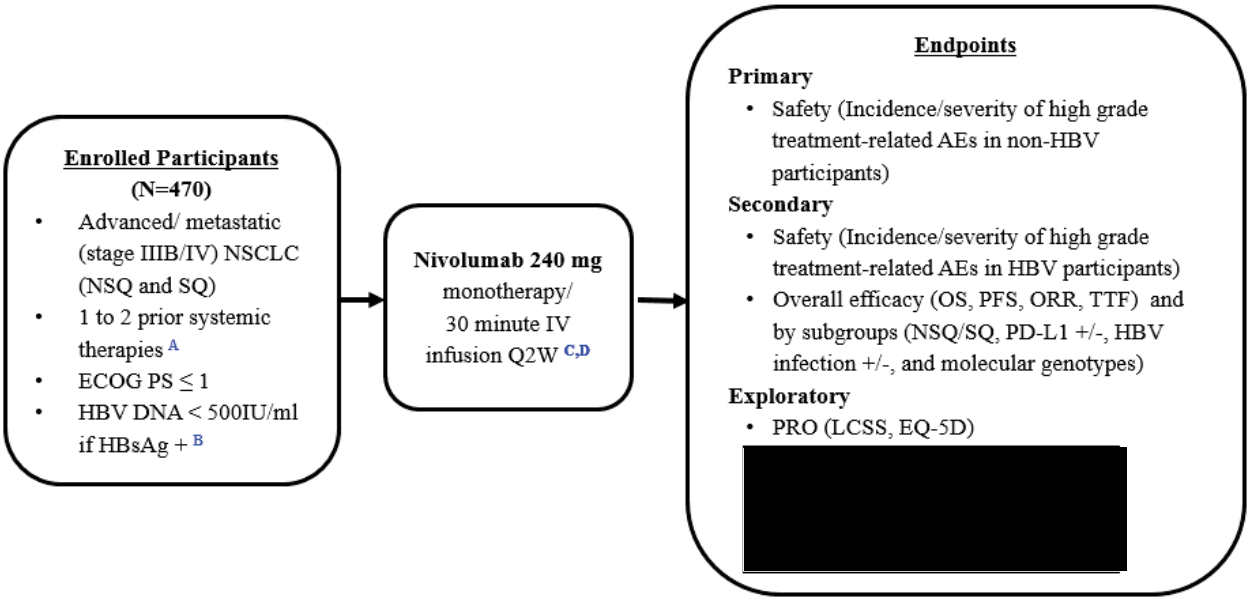
Number of Participants: Approximately 400 treated participants

Treatment Arms and Duration: The primary analysis of safety will be conducted after a minimum of six months after last patient first treatment (LPFT). This study will end when analysis of the primary endpoint is complete. The study will close after the LPFT completes 2 year follow-up.

Study treatment:

Study Drug for CA209870		
Medication	**Potency**	**IP/Non-IP**
nivolumab	100 mg (10 mg/mL and 40 mg/4 mL)	IP

Study Schematic for CA209870



A Enrolled patients without EGFR mutation and ALK-positive are restricted to have only 1 prior systemic therapies. Patients with EGFR mutation or ALK-positive should be treated with prior 2 systemic treatment including TKI and chemotherapy. With a large percentage of NSCLC of patients with EGFR mutation (approximately 30% incidence), this population will be capped to 40 participants in the CA209870 study.

B HBsAg+ participants (estimated 15%) must be on antiviral therapy based on China anti-HBV guideline. Patients with HBV infection will be capped to 60 participants.

C Treatment until progression or unacceptable toxicity. Nivolumab treatment will be given up to 24 months in the absence of disease progression or unacceptable toxicity. Treatment with nivolumab could be reinitiated as per the initial schedule for subsequent disease progression and administered for up to 1 additional year.

D Participants may receive nivolumab treatment beyond progression as defined in protocol. The decision to continue treatment beyond initial progression should be discussed with the BMS Medical Monitor and documented in the study records.

Eligible participants will receive nivolumab (BMS-936558) administered IV with a flat dose of 240 mg q2 weeks as a 30-minute IV infusion on Day 1 of each treatment cycle. Participants will be treated until progression, unacceptable toxicity, withdrawal of consent, or when the study ends, whichever occurs first. Nivolumab treatment will be given up to 24 months in the absence of disease progression or unacceptable toxicity. Treatment with nivolumab could be reinitiated as per the initial schedule for subsequent disease progression and administered for up to 1 additional year. The total duration of the study is expected to be approximately 3 years from the time of first visit of the first participant to the last participant last visit. Efficacy will be evaluated using RECIST 1.1 response criteria.

2. SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline

Procedure	Screening Visit	Notes
Eligibility Assessments		
Informed consent	X	
Inclusion/Exclusion criteria	X	All inclusion/exclusion criteria should be assessed at screening and confirmed prior to first dose.
Medical history	X	Including smoking history. In addition, mutational status of EGFR, ALK, ROS, MET, KRAS and BRAF should be collected, if available. If mutational status is not available in the medical history of participants with non-squamous histology, EGFR and ALK mutational status must be determined as specified in inclusion criteria
Safety Assessments		
Pregnancy test	X	WOCBP only: Serum or urine to be done at screening visit and repeated within 24 hours of first dose of study therapy. Pregnancy testing must use same method throughout study.
Concomitant medications	X	Within 14 days prior to treatment
Physical examination	X	Includes height, weight, baseline EKG, and a focused physical exam is to be performed at screening. C1D1 weight is to be used as baseline weight.
Vital signs	X	Temperature, BP, HR, RR, O_2 saturation by pulse oximetry at rest. Monitor amount of supplemental oxygen, if applicable. Obtain vital signs at screening visit and within 72 hours of treatment
Performance Status	X	Within 14 days prior to treatment.
Serious Adverse Event Assessment	X	Serious Adverse Events from time of consent
Adverse Events	X	Adverse Events from time of consent
Assessment of signs and symptoms	X	Within 14 days prior to treatment
Laboratory Tests		
Hematology and chemistry	X	Laboratory assessments will be performed locally within 14 days prior to treatment.

Table 2-1: Screening Procedural Outline		
Procedure	**Screening Visit**	**Notes**
		See Section 9.4.3 Clinical Safety Laboratory Assessments
Hepatitis B and hepatitis C testing	X	Hepatitis B and C testing (HBV sAg and HCV Ab or HCV RNA). Within 28 days prior to treatment:
HIV Testing	X	Testing for HIV must be performed. Within 28 days prior to treatment:
Thyroid function testing	X	Thyroid panel including TSH, free T3, and free T4 within 14 days prior to treatment
[redacted]		
Tissue collection		
PD-L1 testing and molecular testing	X	Mandatory tumor tissues may be archival or recent sample. One formalin-fixed paraffin embedded tumor tissue block (< 1 year old) or 10 minimum FFPE unstained slides (< 6 months old) must be submitted. A copy of the original pathology report must be submitted with the tissue sample. Additional testing will include EGFR mutation, ALK translocation, [redacted]. Tissue samples from different biopsy procedures are to be submitted if available with each matching pathology report and biopsy date.
Efficacy Assessments		
Radiographic tumor assessment	X	• Solid Tumor: CT with IV contrast of chest/abdomen/pelvis and all other known/suspected sites of disease should be imaged during the screening period. If CT iodinated contrast is contraindicated, CT without IV contrast of chest and MRI with contrast of abdomen and pelvis may be obtained. • Brain MRI without and with contrast should be performed during screening in participants with known history of treated brain metastases or suspected CNS involvement to rule out active brain metastases. • Radiographic tumor assessment must be performed within 28 days prior to first treatment.
IRT/Clinical Drug Supplies		
Contact IRT	X	IRT contact must occur as follows: • For participant number assignment at the time informed consent is obtained. • Before dosing for study drug vial assignment

Table 2-2: On-Treatment Assessment CA209870

Procedure	Cycle 1 Day 1 (Q2 weeks)	Subsequent cycles (Q2 weeks)	Notes
Safety Assessments			
Pregnancy test	X	X	WOCBP only: Serum or urine (for WOCBP only) test to be performed within 24 hours prior to first dose. Serum or urine pregnancy test to be done every 4 weeks (± 1 week) regardless of dosing schedule. Pregnancy testing must use same method as screening/baseline.
Physical examination	X		Including height and weight within 3 days prior to treatment. C1D1 weight is to be used as baseline weight
Targeted physical examination		X	Targeted examination must be performed within 3 days prior to dosing and to include at a minimum the cardiovascular, gastrointestinal, and pulmonary body systems
Vital signs	X	X	Temperature, BP, HR, RR, O_2 saturation by pulse oximetry at rest. Monitor amount of supplemental oxygen, if applicable.
Performance status	X	X	See Appendix 5 for ECOG performance status
Concomitant medication	X	X	
Serious Adverse Events assessment	Continuously		Adverse events and laboratory values will be graded according to the NCI-CTCAE version 4.
Adverse Events assessment	Continuously		Adverse events and laboratory values will be graded according to the NCI-CTCAE version 4.
Laboratory Assessments			
Hematology and chemistry	X	X	Laboratory assessments will be performed locally and within 3 days prior to treatment. See Section 9.4.3 Clinical Safety Laboratory Assessments Note: Cycle 1 Day 1 laboratory assessments do not need to be repeated if performed within 14 days prior to 1st dose.
Thyroid function testing	X	X	Thyroid function testing (TSH with free T3 and free T4) is to be done every 6 weeks (every 3 infusions) Note: Cycle 1 Day 1 laboratory assessments do not need to be repeated if

Table 2-2: On-Treatment Assessment CA209870

Procedure	Cycle 1 Day 1 (Q2 weeks)	Subsequent cycles (Q2 weeks)	Notes
			performed within 14 days prior to 1st dose.
[redacted]			
Efficacy Assessments			
Radiographic tumor assessment	X	X	First tumor assessment should first be performed at 8 weeks (±7 days) from treatment initiation Tumor assessments will occur every 8 weeks (± 1 week). After 48 weeks, tumor assessments will occur every 12 weeks (± 1 week), until disease progression is documented or treatment is discontinued (whichever occurs later). Tumor assessments must use same imaging method as was used at screening/baseline. Participants with a history of brain metastasis should have surveillance MRI approximately every 8 weeks for first 48 weeks and every 12 weeks thereafter. Assessments should include chest, pelvis and abdomen (with contrast) as well as any area that is being monitored. Tumor assessments will use RECIST 1.1 criteria (Appendix 6)

Table 2-2: On-Treatment Assessment CA209870

Procedure	Cycle 1 Day 1 (Q2 weeks)	Subsequent cycles (Q2 weeks)	Notes
Outcome Research Assessment			
LCSS and EQ-5D questionnaires	X	X	For C1D1, PRO must be performed prior to first dose (day -3 to 1) Assessments will be performed every 4 weeks on day 1 (±5 days) for the first 6 months on study, then every 6 weeks for the remainder of the study. At study visits, PRO assessments should be assessed prior to any study related procedures and treatment. See Table 9.10-1
Clinical Drug Supplies and Study Drug Administration			
Nivolumab 240 mg Q2 weeks	X	X	Within 3 days from vial allocation, the participant must receive the first dose of study medication. Participants may be dosed no less than 12 days between doses and within 3 days from the scheduled dose Nivolumab treatment until disease progression, discontinuation due to unacceptable toxicity, withdrawal of consent, or study closure.
IRT/Clinical Drug Supplies			
Contact IRT	X	X	Dosing must be performed within 3 days of study drug vial assignment

Table 2-3: Follow-up Assessments CA209870

Procedure	Follow-up Visits X01 (Day 35) (± 7 Days) and X02 (Day 100)[a] (± 7 Days) after Last Dose	Survival Follow-up Visits[b] Every 12 Weeks	Notes
Safety Assessments			
Targeted Physical Examination	X		Targeted examination must include the cardiovascular, gastrointestinal, and pulmonary body systems and examination to specific malignancy To assess for potential late emergent study drug related findings.
Adverse Events assessment	X		All AEs and SAEs must be collected up to 100 days after study drug discontinuation. SAEs that relate to any later protocol specified procedure must be collected.
Any subsequent cancer treatment information	X	X	
Vital signs	X		28 days from the date of last study treatment
Laboratory Tests			
Hematology and chemistry	X		Laboratory assessments will be performed locally. See Section 9.4.3
Thyroid function testing	X		TSH with free T3 and free T4
Pregnancy test	X		WOCBP only: serum or urine
Outcome Research Assessment			
LCSS and EQ-5D questionnaire	X	X	Both LCSS and EQ-5D will occur in FU Visits 1 & 2. During Survival Visits, the EQ-5D will be collected every 3 months (± 14 days) for the first year of Survival Phase, then every 6 months thereafter. May be obtained through a telephone call or clinic visit. See Table 9.10-1

Table 2-3: Follow-up Assessments CA209870

Procedure	Follow-up Visits X01 (Day 35) (± 7 Days) and X02 (Day 100)[a] (± 7 Days) after Last Dose	Survival Follow-up Visits[b] Every 12 Weeks	Notes
Efficacy Assessments			
Radiographic tumor assessment	X	X	Only for participants without progression. Use same imaging method as was used at screening/baseline.
Participant status	X	X	Every 3 months after X02; may be accomplished by visit or phone contact, to update survival information

[a] Participants must be followed for at least 100 days after last dose of study treatment. Follow-up visit number one X01 (FU1) occurs approximately 35 days (± 7 days) after the last dose or coinciding with the date of discontinuation (± 7 days) if date of discontinuation is greater than 30 days after last dose. Follow-up visit X02 (FU2) occurs approximately 100 days (± 7 days) from last dose.

[b] Survival Follow-up visits to occur every 3 months from Follow-up Visit 2. First Survival visit to occur 3 months (±14 days) from Follow-up visit 2. BMS may request that survival data be collected on all treated participants outside of the protocol window. At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contacts.

3. INTRODUCTION

3.1 Study Rationale

The main objective of the study is to collect additional safety data on the incidence rate of high-grade select AEs and their outcomes and supplement the growing safety database of nivolumab-treated participants. This study will treat approximately 400 participants in order to estimate the incidence of the rare high grade (CTCAE V4 Grades 3-4 and Grade 5) treatment-related select AEs with greater precision and characterize their outcome. Previous studies have shown an incidence per event type between 0 to 3% in NSCLC patients treated with nivolumab monotherapy.

3.1.1 Rationale for Participant Population with NSCLC

Substantial monotherapy clinical activity has been observed in participants with heavily pretreated advanced NSCLC in the ongoing phase 1/2 study of nivolumab (CA209003). This study showed ORR of 17% which is greater than the historical ORR for docetaxel as second line therapy for advanced NSCLC (approximately 8 to 10%).[1,2,3] Durable responses were observed in both squamous and non-squamous subtypes. In 3 mg/kg group, ORR in squamous and non-squamous subgroups was 22% and 26% respectively and 3mg/kg group had median OS of 14.9 months. Whereas, the historical median OS for docetaxel was about 8 months.[4,5,6] Nivolumab phase 3 second-line studies with docetaxel as comparator. CA209017 for squamous NSCLC and CA209057 for non-squamous NSCLC demonstrated significant survival benefit of nivolumab with a better safety profile in nivolumab arm compared to the docetaxel arm.[7,8] Therefore, CA209870 will test the safety and efficacy of nivolumab as monotherapy in previously treated advanced or metastatic NSCLC in in Asia population.

3.1.2 Rationale for Flat Dosing of Nivolumab

The dose and schedule of nivolumab 3 mg/kg every 2 weeks was based upon a 24 February 2012 analysis of safety, efficacy, and exposure-response data from the ongoing phase 1 study, MDX1106-03. Anti-tumor activity was observed in NSCLC participants at dose levels of 1, 3, and 10 mg/kg every 2 weeks. Anti-tumor activity appeared to approach a plateau at dose levels of 3 mg/kg and above. Consistent with these observations, the results of exposure response analyses showed that the probability of a tumor response tended to approach a plateau for trough concentrations produced by 3 mg/kg and 10 mg/kg administered every 2 weeks. Nivolumab was adequately tolerated up to 10 mg/kg, the highest dose level tested, and no maximum tolerated dose (MTD) was identified. While the spectrum, frequency, and severity of nivolumab-related AEs were generally similar across the dose levels tested, the 10 mg/kg dose level had numerically higher rates of Grade 3/4 drug-related SAEs and AEs leading to discontinuation. Based on these observations, a dose of 3 mg/kg every 2 weeks was chosen for further studies.

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 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 to 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 dosing will be similar to that of 3 mg/kg nivolumab dosing.

3.1.3 Rationale for Two Year Duration for Nivolumab Treatment

The optimal duration of immunotherapy is currently unknown. However, because immunotherapy engages the immune system to control the tumor, continuous treatment as is required with targeted agents or cytotoxic therapy may not be necessary. Accumulating evidence from different clinical trials in different tumors types with nivolumab or nivolumab combined to ipilimumab indicates that most of the responses are generally occurring early, with a median time to response of 2-4 months including in patients with NSCLC[9,10,11] and a recent analysis in a melanoma study suggests the majority of patients who discontinue nivolumab and/or ipilimumab for toxicity maintain disease control in the absence of further treatment.[12]

For these reasons, study CA209870 will treat participants with nivolumab for up to 24 months in the absence of disease progression or unacceptable toxicity. Treatment with nivolumab could be reinitiated as per the initial schedule for subsequent disease progression and administered for up to 1 additional year.

3.1.4 Rationale for Safety Data Collection in HBVsAg Positive Patients

According to the data from Shanghai Chest Hospital, 15% Chinese lung cancer patients have HBV sAg positive results, therefore it is anticipated that approximately 60 HBV infected patients will enroll and receive nivolumab treatment. Safety will be evaluated in this population with great interest in hepatic safety and disease related issues.

Data to support inclusion of HBV patients (less than 500 IU/ml) is based on recent analysis of safety data from HBV infected patients with hepatocellular carcinoma in study CA 209040. Results of an interim analysis were published at ASCO 2016 (data on file). Among 214 patients enrolled in this phase 1/2 HCC study, there were 51 HBV-HCC patients. The most common treatment-related AEs TRAEs) were pruritus (22%), fatigue (14%) and rash (12%), which was consistent with that observed in cohorts of other etiology. To note, elevations of AST and ALT were the most frequent Grade 3-4 TRAEs and were more commonly observed in patients with HBV infection. In a total of 22 treated patients, HBV DNA > 100 IU/ml at any time points from the screening to the follow-up was observed. Among them, HBV DNA load was recorded < 500IU/ml in 16, and within 500-1000IU/ml in the other 6 patients. Among these patients, 5 had reported AEs related to abnormal liver function tests (LFT) with only 1 patient in whom Grade 1 abnormal LFT was attributable to study drug according to the investigator. Therefore, no significant safety concern was observed so far in patients with detectable HBV DNA in CA209040.

3.1.5 Rationale for EGFR Mutation and ALK Translocation Patients

Nivolumab is approved by FDA for metastatic NSCLC patients with EGFR or ALK genomic tumor aberrations who have had disease progression on FDA approved therapy for these aberrations.

Clinical benefit of nivolumab was shown in NSCLC patients with EGFR mutation in early phase studies CA209003 (phase 1/2) and CA209012 (phase 1) with objective response rate as 17% and 14% respectively, the safety profile of patients with EGFR mutation is as good as the patients with EGFR wild type.[13] In a second-line phase 3 trial for non-squamous NSCLC including patients with EGFR mutation (CA209057), the patients reported outcome based on EQ-5D and LCSS in nivolumab treated patients is better than the patients treated by docetaxel.

In addition, almost all patients who initially respond to EGFR TKI or ALK TKI will subsequently develop disease progression. Although part of the patients could get benefit from second and third generation TKIs overcoming resistance, it is still a population with highly unmet medical needs.

With a large percentage of NSCLC of patients with EGFR mutation (approximately 30% incidence), this population will be capped to 40 participants in the CA209870 study.

3.1.5.1 Rationale for Nivolumab 30 Minute Infusion

Long infusion times place a burden on patients and treatment centers. Establishing that nivolumab can be safely administered using shorter infusion times of 30 minutes duration in subjects will diminish the burden provided no change in safety profile. The incidence rate of treatment related select high grade AE is 0.5 to 3% of nivolumab 3mg/kg every two weeks with infusion time no less than 30 minutes based on the Checkmate 153 study which published in ASCO 2016.[14] Previous clinical studies show that nivolumab has been administered safely over 60 minutes at doses ranging up to 10 mg/kg over long treatment duration. In Study CA209010 (a phase 2, randomized, double blinded, dose-ranging study of nivolumab in subjects with

advanced/metastatic clear cell RCC), a dose association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg and 18.5% at 10 mg/kg). All the events were Grade 1 - 2 and were manageable. An infusion duration of 30 minutes for 240mg nivolumab (40% of the dose provided at 10 mg/kg in patients with a body weight expected to be on average around 60 kg) is not expected to present any safety concerns compared to the prior experience at 10 mg/kg nivolumab dose infused over a 60-minute duration. Overall, infusion reactions including high-grade hypersensitivity reactions have been uncommon across nivolumab clinical studies. A change in safety profile is not anticipated with 30-minute infusion of nivolumab.

3.1.5.2 Rationale for Biomarker Assessments

Aberrant expression of PD-L1 protein by tumor cells (retrospectively detected by IHC) has been reported in a number of human malignancies, especially in relation to poor prognosis in multiple tumor types, including squamous cell and non-squamous NSCLC.[15,16,17,18,19,20,21] These findings may be explained by the notion that high PD-L1 expression leads to immune evasion. This hypothesis is supported by separate studies demonstrating that PD-L1 expressed by tumor cells enhances apoptosis of activated tumor-specific T cells in vitro and that the expression of PD-L1 protects tumor cells from the induction of apoptosis by effector T cells.[22] In NSCLC, blocking PD-L1 allows for the increase of tumor-infiltrating CD8+ T cells and an increased production of IFN-γ but no difference noted in peripheral blood CD8+ T cells when subjects with NSCLC were compared with healthy controls.[23] These high levels of PD-L1 protein expression in NSCLC have also been significantly associated with poor prognosis and the presence of tumor infiltration by immature dendritic cells.[24]

Intriguingly, preliminary data indicate that PD-L1 protein expression in tumors may correlate with nivolumab clinical activity. Archival tumor specimens from a limited subset (N = 30) of subjects in MDX1106-03 were assessed for tumor PD-L1 protein expression measured by immunohistochemistry (IHC). In this subset, 100% of subjects whose tumors lacked detectable expression of PD-L1 protein (N = 13) did not have evidence of clinical benefit (response, stable disease, or mixed response) to nivolumab, whereas subjects whose tumors were deemed PD-L1- positive (based on PD-L1 protein expression on a pre-defined threshold of tumor cells) were more likely to demonstrate clinical benefit. Despite the limited number of subjects evaluated in this initial study, our findings indicate that tumor PD-L1 protein expression status may have a profound impact on the likelihood of a patient to respond to nivolumab therapy. Because clinical benefit appeared to correlate with PD-L1 status measured in baseline, pre-treatment specimens, these data also suggest that PD-L1 expression could serve as a predictive biomarker for patient selection. As such, analysis of a larger number of samples is warranted, and evaluation of additional patients (and their tumors) enrolled in the MDX1106-03 study is ongoing.

In this trial, baseline tumor tissue will be collected for biomarker analyses. [redacted]

[redacted]

3.1.5.3 Rationale for Outcomes Research Assessments

The evaluation of health related quality of life is an increasingly important aspect of a clinical efficacy in oncology trials. Such data provides an understanding of the impact of treatment from the patient perspective and offers insights into the patient experience that may not be captured through physician reporting. [redacted]

3.2 Background

OPDIVO® (nivolumab), is a human programmed death receptor-1 (PD-1)[25] blocking antibody approved for unresectable or metastatic melanoma, previously treated metastatic squamous NSCLC, advanced renal cell carcinoma, and classical Hodgkin lymphoma in the United States and in Japan for unresectable melanoma, kidney cancer, and NSCLC, and is in clinical development for the treatment of other malignancies. Nivolumab has also demonstrated clinical activity as combination therapy with ipilimumab in melanoma, NSCLC, RCC, and Hodgkin lymphoma. The majority of responses were durable and exceeded 6 months.

The overall safety experience with nivolumab, as a monotherapy or in combination with other therapeutics, is based on experience in approximately 12,300 subjects treated to date. Overall, the safety profile of nivolumab monotherapy is manageable and generally consistent across completed and ongoing clinical trials with no maximum tolerated dose (MTD) reached at any dose tested up to 10 mg/kg. There was no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. Most AEs were low grade (Grade 1 - 2) with relatively few related high grade (Grade 3 - 4) AEs.

To characterize AEs of special clinical interest that are potentially associated with the use of nivolumab, Bristol-Myers Squibb has identified select AEs based on the following principles: AEs that may differ in type, frequency, or severity from AEs caused by therapies that are not immuno-modulating; AEs that may require immunosuppression (eg, corticosteroids) as part of their management; AEs whose early recognition and management may mitigate severe toxicity; AEs for which multiple event terms may be used to describe a single type of AE, thereby necessitating the pooling of terms for full characterization.

Based on these principles and taking into account the types of AEs already observed across studies of nivolumab monotherapy, pneumonitis, interstitial nephritis, diarrhea/colitis, hepatitis, rash, endocrinopathies, and hypersensitivity/infusion reaction events are currently considered to be select AEs. The majority of these AEs have been managed successfully with supportive care and, in more severe cases, a combination of dose delay, permanent discontinuation, and/or initiation of systemic corticosteroids.

This protocol will generate safety and efficacy data on nivolumab monotherapy for advanced and metastatic NSCLC.

Mechanism of action of nivolumab: Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses.[26,27,28] Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor (TCR).[29] 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.[30] PD-1 signaling has been shown to inhibit CD28-mediated upregulation of IL-2, IL-10, IL-13, interferon-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.[31] 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 (EC50 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (IC50 ± 1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4 and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction (MLR). Using a CMV re stimulation assay with human PBMC, the effect of nivolumab on antigen specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV specific memory T cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and result in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[32]

A detailed description of the chemistry, pharmacology, efficacy, and safety of nivolumab is provided in the BMS-936558 (nivolumab) Investigator Brochure.[33]

3.3 Benefit/Risk Assessment

Nivolumab has been studied in over 12,300 subjects and is widely approved in multiple indications. Across multiple tumor types, nivolumab has demonstrated an acceptable benefit-risk ratio with clinical activity and tolerable AE profile, including advanced melanoma, HCC, CRC, NSCLC, and some lymphomas.

Subjects with advanced NSCLC who progressed after first-line therapy represent a great unmet medical need. The clinical activity of nivolumab in this patient population shows significantly improved clinical outcomes as monotherapy compared with docetaxel in both squamous and non-squamous NSCLC.

Docetaxel has a well characterized adverse event profile as cytotoxic chemotherapy, including the potential of pancytopenia, fluid retention, peripheral neuropathies, diarrhea, nausea, and vomiting. In CA209017 and CA209057, nivolumab demonstrated improved safety profile compared with docetaxel. Immune mediated adverse events of nivolumab are consistent with its mechanism of action and include liver toxicities (eg, ALT or AST increase), endocrinopathies (eg, hypothyroidism), pulmonary toxicity (eg, pneumonitis), renal toxicity (eg, nephritis), skin toxicity (eg, rash), and gastrointestinal toxicity (eg, diarrhea).

The data of CA209040 showed the safety profile of nivolumab is tolerable of the HCC patients with HBV infection, even the HBV DNA is more than 500IU/ml, so we choose HBV DNA <500IU/ml if HBVsAg positive. Based on the PPK modeling and CA209153 data, nivolumab 240 mg and infusion time with 30 minutes are well tolerated. The majority of the immune mediated adverse events are of low grade. Guided by the established toxicity management algorithm immune mediated adverse events are well manageable.

The manageable AEs profile observed with nivolumab, including the EGFR mutation and ALK rearrangment population, supports a phase 3b clinical trial of nivolumab monotherapy as 240 mg intravenous with the infusion time of 30 minutes every 2 weeks in second-line advanced or metastatic NSCLC without EGFR mutation or ALK translocation, and third-line advanced or metastatic NSCLC with EGFR mutation or ALK translocation.

To assure an ongoing favorable benefit-risk assessment for subjects enrolled onto CA209870, a delegated internal physician will monitor the activity and safety throughout the conduct of the trial. Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the BMS-936558 (nivolumab) Investigator Brochure.[33]

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate safety and tolerability in non-HBV infected participants with advanced or metastatic NSCLC who have progressed during or after one prior systemic therapy and are treated with nivolumab monotherapy with an infusion duration of 30 min	• Incidence and severity of high grade (combined CTCAE v4 Grade 3-4 and Grade 5) treatment-related select adverse events in non-HBV infected patients.
Secondary	
• To assess safety and tolerability in HBV infected participants with advanced or metastatic NSCLC who have progressed during or after one prior systemic therapy and are treated with nivolumab monotherapy with an infusion duration of 30 min	• Incidence and severity of all high grade (combined CTCAE v4 Grade 3-4 and Grade 5) treatment-related select adverse events in HBV participants
• To assess safety and tolerability in all participants	• Incidence and severity of AEs and specific laboratory abnormalities in all treated subjects
• To evaluate efficacy in participants with advanced or metastatic NSCLC who have progressed during or after one prior systemic therapy and are treated with nivolumab monotherapy	• Collection of overall survival (OS), time to treatment failure (TTF), progression free survival (PFS), objective response rate (ORR) , duration of tumor response (DOR) by tumor histology (SQ or NSQ), tumor PD-L1 expression level (PD-L1 negative or PD-L1 positive), by infection status (HBV infection or non-HBV infection), and by molecular type (EGFR mutation, ALK translocation, or WT).
• **Exploratory**	
• To assess overall health status and health utility	• The 3-level version of the EQ-5D (EQ-5D-3L) visual analog scale (VAS) and utility index, respectively
• To evaluate the proportion of participants exhibiting disease-related symptom deterioration by Week 12 and by Week 24	• Lung Cancer Symptoms Scale (LCSS) will use disease-related symptom deterioration rate at week 12 and week 24 and is defined as the proportion of treated subjects who had 10 points or more increase from baseline in Average Symptom Burden Index (ASBI) score at any time between first dosing and at week 12 and week 24.
[redacted]	

[redacted]

5. STUDY DESIGN

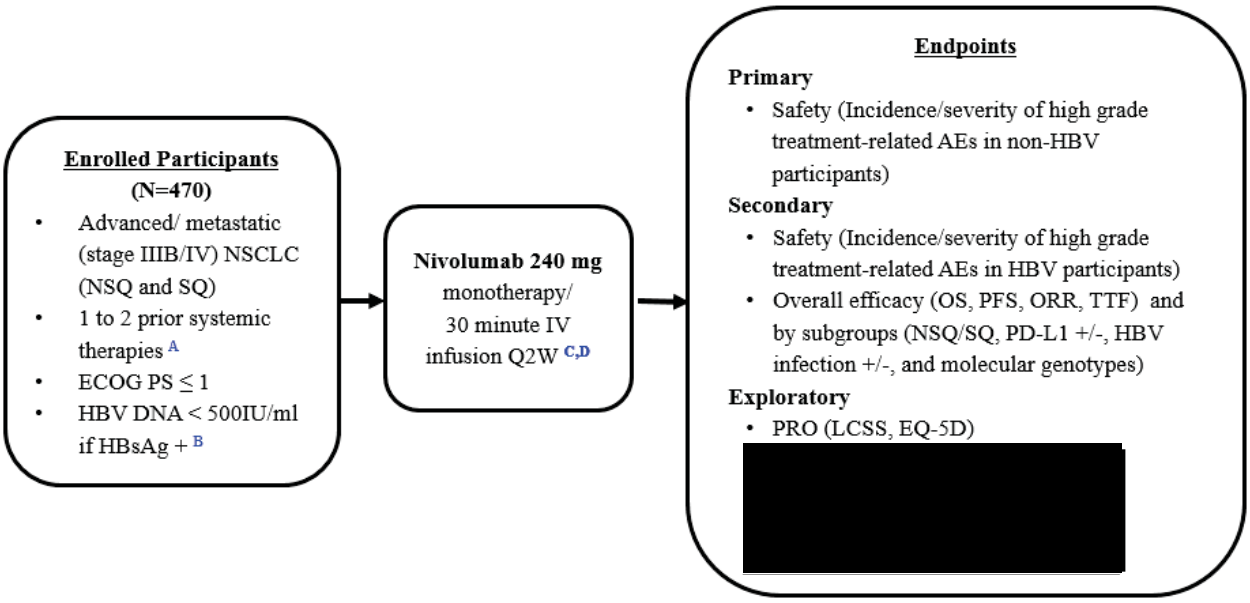
5.1 Overall Design

In this safety study of nivolumab monotherapy, subjects will undergo screening evaluations to determine eligibility within 28 days prior to first dose. Eligible subjects will be treated with nivolumab administered intravenously over 30 minutes at 240 mg every two weeks. Each 2 week dosing period will constitute a cycle.

Study treatment can continue beyond initial investigator assessed progression, as specified in criteria presented in Section 7.4.4 Treatment beyond Disease Progression. The study will close after the last enrolled subject completes 2 year follow up. Details regarding the assessments to be performed during these phases are outlined in Section 2 Schedule of Activities.

The study design schematic is presented in Figure 5.1-1.

Figure 5.1-1: Study Design Schematic



A Enrolled patients without EGFR mutation and ALK-positive are restricted to have only 1 prior systemic therapies. Patients with EGFR mutation or ALK-positive should be treated with prior 2 systemic treatment including TKI and chemotherapy. With a large percentage of NSCLC of patients with EGFR mutation (approximately 30% incidence), this population will be capped to 40 participants in the CA209870 study.

B HBsAg+ participants (estimated 15%) must be on antiviral therapy based on China anti-HBV guideline. Patients with HBV infection will be capped to 60 participants.

[C] Treatment until progression or unacceptable toxicity. Nivolumab treatment will be given up to 24 months in the absence of disease progression or unacceptable toxicity. Treatment with nivolumab could be reinitiated as per the initial schedule for subsequent disease progression and administered for up to 1 additional year.

[D] Participants may receive nivolumab treatment beyond progression as defined in protocol. The decision to continue treatment beyond initial progression should be discussed with the BMS Medical Monitor and documented in the study records.

Physical examinations, vital sign measurements, outcome questionnaires, [redacted] and clinical laboratory evaluations will be performed at selected times throughout study participation. Participants will be closely monitored for AEs throughout the study. Blood samples will be collected for safety [redacted] analysis.

In this study, overall survival is a key 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 drug must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 8 until death or the conclusion of the study.

5.1.1 Data Monitoring Committee and Other External Committees

A Data Monitoring Committee (DMC) will not be used for this study, given the following:

1) This study is an open-label, single arm study.
2) Safety data will be closely monitored by BMS with real time review and assessment of SAEs as they are received, and periodic review safety signals.

BMS will assign a physician responsible for reviewing, on a systematic and continuous basis, the safety of participants on this study. This includes a review of serious and non-serious adverse events, and all hematological and non-hematological events. In addition, BMS has a Medical Surveillance Team (MST), independent from the clinical medical monitor. The MST has the primary responsibility within Bristol-Myers Squibb for assessing emerging safety trends, identifying potential safety signals, notifying appropriate stakeholders of relevant findings, and implementing risk mitigation activities to ensure the safety of patients participating in BMS trials. The MST is also responsible for reviewing data from all sources including non-clinical studies and clinical trials, monitoring the progress of various nivolumab (BMS-936558) safety support activities, and recommending and implementing necessary changes to the safety plan and any other specific safety-related activities.

5.2 Number of Participants

Approximately 470 participants will be screened for the trial to enroll and treat approximately 400 participants. Patients with HBV infection will be capped to 60 participants according to the prevalence of HBV infection in China (~15% prevalence in China NSCLC population).

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 or scheduled procedure shown in the Schedule of Activities for the last participant. Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected, if this is not the same

5.4 Scientific Rationale for Study Design

The main objective of the study is to provide additional insight into the frequency of high-grade select AEs and their outcome, and thus supplement the growing safety database of nivolumab treated Asian subjects. This study will treat approximately 400 Asian subjects in order to estimate the incidence of the rare high grade (CTCAE V4 Grade 3-4 and Grade 5) treatment-related select AEs with greater precision and characterize their outcome (between 0 and 2% incidence per event type in NSCLC subjects treated with nivolumab monotherapy in previous studies). The safety assessment for the patient with HBV infection (HBV DNA < 500 IU/ml) is expected to be similar and limited to 60 treated subjects. These data will provide a larger data set to inform the risk/benefit profile of the use of nivolumab in Asian NSCLC patients and will help to further clarify the effectiveness of the current treatment algorithms for managing drug-mediated toxicities.

5.5 Justification for Dose and Infusion Time

Eligible subjects will be treated with nivolumab administered intravenously over 30 minutes at 240 mg every two weeks. Each 2 week dosing period will constitute a cycle. The first dose of study drug is to be administered within 3 days of enrollment confirmation. All subjects will be monitored continuously for AEs while on study treatment. Treatment modifications (eg, dose delay, reduction, or discontinuation) will be based on specific laboratory and adverse event criteria, as described in Sections 7.4.

5.5.1 Summary of Safety of Nivolumab in Metastatic Setting

In clinical trials, nivolumab has demonstrated an acceptable benefit-risk across multiple tumor types, including advanced melanoma, RCC, NSCLC, and some lymphomas. The two clinical trials that have contributed the most to the clinical experiences of nivolumab monotherapy are CA209003 and CA209037. Overall, the safety profile is similar across these two studies and is discussed below. Therefore, no additional degree of safety risk is expected.

CA209003 is a completed phase 1 open label, multiple dose escalation study in 306 subjects with select previously treated advanced solid tumors, including melanoma, RCC, NSCLC, CRC, and hormone-refractory prostate cancer. Subjects received nivolumab at doses of 0.1, 0.3, 1, 3, or 10 mg/kg intravenously every 2 weeks, up to a maximum of 2 years of total therapy. A total of 306 subjects were treated with nivolumab in the dose range of 0.1 to 10 mg/kg.

No maximal tolerated dose was identified in CA209003. The incidence, severity and relationship of adverse events (AEs) were generally similar across dose levels and tumor types. Nivolumab related AEs of any grade occurred in 75.2% of subjects. Of the 306 treated subjects, 303 (99.0%) subjects have at least 1 reported AE regardless of causality. The most frequently reported AEs were fatigue (54.9%), decreased appetite (35.0%), diarrhea (34.3%), nausea (30.1%), and cough (29.4%). Treatment-related AEs were reported in 230 (75.2%) of the 306 subjects. The most frequently reported treatment-related AEs were fatigue (28.1%), rash (14.7%), diarrhea (13.4%), and pruritus (10.5%). Most treatment-related AEs were low grade. Treatment-related high grade (Grade 3 - 4) AEs were reported in 52 (17.0%) subjects. The most common treatment-related high grade AEs were fatigue (2.3%) and diarrhea (1%). Drug-related SAEs occurred in 11.5% of

subjects. Grade 3 - 4 drug-related SAEs reported in at least 2 subjects included: diarrhea (3 subjects, 1.0%), pneumonitis (3 subjects, 1.0%), pneumonia (2 subjects, 0.7%) and lipase increased (2 subjects, 0.7%).

Select AE categories (events with a potential inflammatory mechanism requiring more frequent monitoring and/or unique intervention such as immunosuppressants and/or endocrine replacement therapy) include: GI AEs, pulmonary AEs, renal AEs, hepatic AEs, skin AEs, and endocrinopathies. In addition, select AEs include a category for infusion reaction. Each category is composed of a discrete set of preferred terms, including those of greatest clinical relevance. These select AEs are considered events of interest based on the mechanism of action and were previously referred to as immune-related AEs or immune-mediated AEs. Most high grade events resolved following the treatment guidelines for the treatment of pulmonary events, GI events, hepatic events, renal events, and endocrine events, respectively. Overall, the safety profile at 3 mg/kg (n = 54) was similar to safety profile across the dose ranges from 0.1 mg/kg to 10 mg/kg (n = 306).

Table 5.5.1-1: Treatment-related Select Adverse Events by Treatment - All CTC Grades Reported in at least 10 Treated Subjects in CA209003

Preferred Term	3 mg/kg N = 54		Total (0.1 to 10 mg/kg) N = 306	
	Any Grade	Grade 3 - 4	Any Grade	Grade 3 - 4
Any select AE	23 (43)	2 (4)	140 (46)	19 (6)
Any endocrinopathies	4 (7)	0	29 (10)	3 (1)
Endocrinopathies thyroid	4 (7)	0	26 (9)	2 (1)
Blood TSH increased	2 (4)	0	11 (4)	1 (0.3)
Hypothyroidism	1 (2)	0	11 (4)	1 (0.3)
Any skin AEs	12 (22)	0	75 (25)	1 (0.3)
Rash	5 (9)	0	45 (15)	0
Pruritus	3 (6)	0	32 (11)	1 (0.3)
Any GI AE	7 (13)	0	43 (14)	3 (1)
Diarrhea	6 (11)	0	41 (13)	3 (1)
Any hepatic AE	3 (6)	2 (4)	18 (6)	4 (1)
ALT increased	1 (2)	0	11 (4)	1 (0.3)
Any pulmonary AE	2 (4)	0	17 (6)	6 (2)
Pneumonitis	1 (2)	0	12 (4)	4 (1)
Other select AE	3 (6)	0	15 (5)	2 (1)
Infusion-related reaction	3 (6)	0	12 (4)	0

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; GI, gastrointestinal; TSH, thyroid stimulating hormone Source: CA209003. Clinical data cut-off date: 18-Mar-2013

Total includes subjects who also received 0.1 mg/kg (n = 17), 0.3 mg/kg (n = 18), 1 mg/kg (n = 86), and 10 mg/kg (n = 131) in addition to those illustrated at 3 mg/kg (n = 54).

Treatment-related AEs leading to discontinuation were reported in 32 (10.5%) of the 306 nivolumab treated subjects on CA209003. The most frequent of these were pneumonitis (8 subjects; 2.6%) and colitis (3 subjects; 1.0%). There were 3 (1%) drug related deaths; each occurred after development of pneumonitis.

CA209037 is an ongoing phase 3, open-label study of nivolumab (3 mg/kg administered by intravenous [IV] infusion every 2 weeks [q2w]) vs investigator's choice therapy in subjects with previously-treated advanced melanoma. As of 30-Apr-2014, 268 subjects have been treated with 3 mg/kg IV nivolumab in CA209037 with safety results as outlined below that are consistent with the phase 1 experience of CA209003.

In CA209037, nivolumab related AEs of any grade occurred in 67.5% of subjects. Of the 268 subjects treated with nivolumab, 255 (95.1%) subjects had at least 1 reported AE regardless of causality. The most frequently reported treatment-related AEs were fatigue (25.0%), pruritus (16.0%), diarrhea (11.2%), and nausea (9.3%). Most treatment-related AEs were low grade. Treatment -related high grade (Grade 3 - 4) AEs were reported in 24 (9.0%) of subjects. The most common treatment-related high grade AEs were fatigue (0.7 %), anemia (0.7%), diarrhea (0.4%), and vomiting (0.4%). Drug-related SAEs occurred in 4.5% of subjects. Grade 3 - 4 drug related SAEs reported in at least 2 subjects included diarrhea (2 subjects, 0.7%). In addition, drug-related SAE of hyperglycemia occurred in 0.7%.

Select AE categories (events with a potential inflammatory mechanism requiring more frequent monitoring and/or unique intervention such as immunosuppressants and/or endocrine replacement therapy) were:

- Skin (29.1%) including pruritus (16.0%) and rash (9.3%)
- GI (11.6%) including diarrhea (11.2%) and colitis (1.1%)
- Endocrine (7.8%) including hypothyroidism (7.8%) and hyperthyroidism (1.9%)
- Hepatic (4.5%) including AST increased (4.1%) and ALT increased (2.6%)
- Pulmonary (2.2%) including pneumonitis (1.9%)
- Hypersensitivity/infusion reaction (1.9%)
- Renal (1.5%) including increased creatinine (0.7%), increased urea (0.4%), and tubulointerstitial nephritis (0.4%)

In general, these select AEs were considered by the investigator to be related to study drug, except for AEs in the hepatic and renal select AE categories. There were few high-grade select AEs (n = 20), and the majority of high-grade events (13 of 20) subsequently resolved, including those for which immunosuppressive therapy was not initiated.

Treatment-related AEs leading to discontinuation were reported in 6 (2.2%) of the 268 nivolumab treated subjects in CA209037 including single events of colitis, pancreatitis, increased ALT, increased lipase, autoimmune neuropathy, and demyelination. In CA209037, one subject experienced drug-related grade 5 hypoxia, possibly pneumonitis, in the setting of lymphangitic spread and possible pneumonia.

Taken together, these data from studies from CA209003 and CA209037 highlight the acceptable safety profile with similar trends in AEs in the 574 subjects treated with nivolumab in these 2 studies. Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the nivolumab Investigator Brochure (IB).[33]

5.5.2 Rationale for Nivolumab Flat Dose Selection

The nivolumab dose of 240 mg every 2 weeks (q2w) was selected based on clinical data and modeling and simulation approaches using population PK (PPK) and exposure-response analyses of data from studies in multiple tumor types (melanoma, NSCLC, and RCC) where body weight normalized dosing (mg/kg) has been used.

PPK analyses have shown that the PK of nivolumab is linear with proportional exposure over a dose range of 0.1 to 10 mg/kg, and no differences in PK across ethnicities and tumor types were observed. Nivolumab clearance and volume of distribution were found to increase as the body weight increases, but less than the proportional with increasing weight, indicating that mg/kg dosing represents an over-adjustment for the effect of body weight on nivolumab PK. The PPK model previously developed using data from NSCLC subjects has recently been updated, using data from 1,544 subjects from 7 studies investigating nivolumab in the treatment of melanoma, NSCLC, and RCC. In this dataset, the median (minimum - maximum) weight was 77 kg (35 to 160 kg) and thus, an approximately equivalent dose of 3 mg/kg for an 80 kg subject, nivolumab 240 mg q2w was selected for future studies. To predict relevant summary exposures of nivolumab 240 mg q2w, the PPK model was used to simulate nivolumab 3 mg/kg q2w and 240 mg q2w. In the simulations, the simulated patient populations consisted of 1,000 subjects per treatment arm randomly sampled from aforementioned pooled database of cancer subjects. Because no differences in PK were noted across ethnicities and tumor types, these simulated melanoma and NSCLC data will be applicable to subjects with other tumor types. The simulated measure of exposure of interest, time-averaged concentrations (Cavgss) for 240 mg q2w are predicted to be similar for all subjects in reference to 80 kg subjects receiving 3 mg/kg q2w.

Nivolumab is safe and well tolerated up to 10 mg/kg q2w dose level. AEs have been broadly consistent across tumor types following monotherapy and have not demonstrated clear dose-response or exposure-response relationships. Additionally, the simulated median and 95th prediction interval of nivolumab summary exposures across body weight range (35 - 160 kg) are predicted to be maintained below the corresponding observed highest exposure experienced in nivolumab ie, 95th percentile following nivolumab 10 mg/kg q2w from clinical study CA209003. Thus, while subjects in the lower body weight ranges would have greater exposures than 80 kg subjects, the exposures are predicted to be within the range of observed exposures at doses (up to 10 mg/kg q2w) used in the nivolumab clinical program, and are not considered to put subjects at increased risk. For subjects with greater body weights, the simulated ranges of exposures are also not expected to affect efficacy, because the exposures predicted following administration of a 240 mg q2w are on the flat part of the exposure-response curves for previously investigated tumors, melanoma and NSCLC. Given the similarity of nivolumab PK across tumor types and the similar exposures predicted following administration of 240 mg flat dose compared to 3 mg/kg, it is expected that the safety and efficacy profile of 240 mg

nivolumab will be similar to that of 3 mg/kg nivolumab. Thus nivolumab 240 mg every 2 weeks over 30 minutes will be recommended in this study.

5.5.3 Clinical Pharmacology Summary

The pharmacokinetics (PK) of nivolumab were studied in subjects over a dose range of 0.1 to 10 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. The geometric mean (% CV%) clearance (CL) was 9.5 mL/h (49.7%), geometric mean volume of distribution at steady state (Vss) was 8.0 L (30.4%), and geometric mean elimination half-life (t1/2) was 26.7 days (101%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg q2w, and systemic accumulation was approximately 3-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. The clearance of nivolumab increased with increasing body weight. The PPK analysis suggested that the following factors had no clinically important effect on the CL of nivolumab: age (29 to 87 years), gender, race, baseline lactate dehydrogenase (LDH), PD-L1. A PPK analysis suggested no difference in CL of nivolumab based on age, gender, race, tumor type, baseline tumor size, and hepatic impairment.

Although ECOG status, baseline glomerular filtration rate (GFR), albumin and body weight had an effect on nivolumab CL, the effect was not clinically meaningful. When nivolumab is administered in combination with ipilimumab, the CL of nivolumab was increased by 24%, whereas there was no effect on the clearance of ipilimumab. Additionally, PPK and exposure response analyses have been performed to support use of 240 mg q2w dosing in addition to the 3 mg/kg q2w regimen. Using the PPK model, exposure of nivolumab at 240 mg flat dose was identical to a dose of 3 mg/kg for subjects weighing 80 kg, which was the approximate median body weight in nivolumab clinical trials.

Full details on the clinical pharmacology aspects of nivolumab can be found in the BMS-936558 (nivolumab) Investigator Brochure.[33]

5.5.4 Rationale for 30-Minute Infusion

Long infusion times place a burden on participants and treatment centers. Establishing that nivolumab can be safely administered using shorter infusion times of 30 minutes duration in participants will diminish the burden provided no change in safety profile. Previous clinical studies show that nivolumab has been administered safely over 60 minutes at doses ranging up to 10 mg/kg over long treatment duration. In Study CA209010, (a phase 2, randomized, double blinded, dose-ranging study of nivolumab in participants with advanced/metastatic clear cell RCC) a dose association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg and 18.5% at 10 mg/kg). All the events were Grade 1 - 2 and were manageable. An infusion duration of 30 minutes for 240mg nivolumab (40% of the dose provided at 10 mg/kg in patients with a body weight expected to be on average around 60 kg) are not expected to present safety concerns compared to the prior experience at 10 mg/kg nivolumab dose infused over a 60-minute duration. Overall, infusion reactions including high-grade hypersensitivity reactions have been uncommon across nivolumab clinical studies. A change in safety profile is not anticipated with 30-minute infusion of nivolumab.

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 IRB/IEC-approved written informed consent form in accordance with regulatory and local guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal participant care.
   b) Participants must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests, and other requirements of the study.
2) Type of Participant and Target Disease Characteristics
   a) Participants with histologically- or cytologically-documented NSCLC (SQ or NSQ) who present with Stage IIIB/Stage IV disease (according to version 8 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology), or with recurrent or progressive disease following multimodal therapy (radiation therapy, surgical resection, or definitive chemo-radiotherapy for locally advanced disease).
      i) Participants must have experienced disease progression or recurrence after one systemic therapies for advanced or metastatic disease.
      ii) Each subsequent line of therapy must be preceded by disease progression. A switch of an agent within a regimen in order to manage toxicity does not define the start of a new line of therapy.
      iii) Maintenance therapy following platinum doublet-based chemotherapy is not considered as a separate regimen of therapy.
      iv) 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.
      v) Participants with recurrent disease > 6 months after completing a platinum-containing adjuvant, neoadjuvant or definitive chemoradiation therapy given for locally advanced disease, who also subsequently progressed during or after a systemic regimen given to treat the recurrence, are eligible.
         (1). EGFR testing is not required if ALK or KRAS test is positive.
         (2). ALK testing is not required if EGFR or KRAS test is positive.
   b) Participants with non-squamous histology must be tested for EGFR mutations (including, but not limited to, deletions in exon 19 and exon 21 [L858R] substitution) and ALK rearrangement if tests have not been previously performed. Participants who are positive on sensitizing EGFR mutations (exon 19 deletion, exon 21 [L858R] substitution) or ALK rearrangement testing, are eligible to enroll after progression from first line tyrosine kinase inhibitor (TKI) regimen and one systemic therapies.
      i) Participants who are positive on non-sensitizing EGFR mutation are eligible to enroll after two line of systemic therapy, which can be TKI and chemotherapy.
      ii) Participants are eligible if genetic test results are indeterminate or if no tumor tissue is available or accessible for testing as long as they have received one prior systemic chemotherapy.

iii) Experimental therapies when given as separate regimen are considered as separate line of therapy. Participants with more than 1 line chemotherapy are not allowed in this study.

c) Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 1

d) Participants must have measurable disease by CT or MRI per RECIST 1.1 criteria (radiographic tumor assessment performed within 28 days of first dose of study drug) or clinically apparent disease that the investigator can follow for response per RECIST 1.1.

e) Prior radiotherapy or radiosurgery must have been completed at least 2 weeks prior to starting study treatment

3) Age and Reproductive Status

a) Males and Females, ≥ 18 of age

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

c) Women must not be breastfeeding

d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of study treatment with nivolumab and 5 months after the last dose of study treatment (ie, 30 days [duration of ovulatory cycle] plus the time required for the investigational drug to undergo approximately five half-lives).

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

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.

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.

6.2 Exclusion Criteria

1) Medical Conditions

a) Women with a positive pregnancy test at enrollment or prior to administration of study medication

b) Participants with active CNS metastases are excluded. Participants are eligible if the 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 enrollment. In addition, participants must be either off corticosteroids, or on a stable or decreasing dose of < 10 mg daily prednisone (or equivalent).

c) Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of first dose of study drug. Inhaled or topical steroids, and adrenal replacement

steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

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

e) Participants with carcinomatous meningitis.

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

g) Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the subject to receive protocol therapy, or interfere with the interpretation of study results.

h) Participants with an active, known or suspected autoimmune disease. Participants with type I diabetes mellitis, 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.

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

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

k) Participants who have been previously treated with cell immunotherapy (eg, cytokine induced killer [CIK] treatment).

l) Participants who participated in either arm of the following clinical trials CA209078 or received prior treatment with anti-PD-1 or anti-PDL1 experimental agents.

m) Participants who participated in other experimental therapies for NSCLC.

2) Prior/Concomitant Therapy

a) Participants who received 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) Participants with a history of screen failure to any PD1 or PDL1 antibody clinical trial due to PD-L1 status. Patients with undetermined status are allowed on study.

c) All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to Grade 1 (NCI CTCAE version 4) or baseline before administration of study drug. Participants with toxicities attributed to prior anti-cancer therapy which are not expected to resolve and result in long lasting sequelae, such as neuropathy after platinum based therapy, are permitted to enroll.

d) Treatment with any chemotherapy, radiation therapy, biologics for cancer, or investigational therapy within 28 days of first administration of study treatment

(participants with prior cytotoxic or investigational products < 4 weeks prior to treatment might be eligible after discussion between investigator and sponsor, if toxicities from the prior treatment have been resolved to Grade 1 (NCI CTCAE version 4).

e) Previous treatment with an investigational agent

f) Current or planned anti-cancer treatments

3) Physical and Laboratory Test Findings

a) Screening laboratory values must meet the following criteria (using CTCAE v4):

i) WBC < 2000/uL

ii) Neutrophils < 1500/uL

iii) Platelets < 100 $x10^3$/uL

iv) Hemoglobin < 9.0 g/dL

v) Serum creatinine > 1.5 x ULN or calculated creatinine clearance < 40 mL/min (using the Cockcroft Gault formula)

Female CrCl = ([140 - age in years] x weight in kg x 0.85)/ (72 x serum creatinine in mg/dL)

Male CrCl = ([140 - age in years] x weight in kg x 1.00)/ (72 x serum creatinine in mg/dL)

vi) AST > 3.0 x ULN

vii) ALT > 3.0 x ULN

viii) Total Bilirubin > 1.5 x ULN (except participants with Gilbert Syndrome who must have a total bilirubin level of < 3.0 x ULN).

b) HBV DNA test for participants with HBsAg positive should > 500 IU/ml

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

d) Any positive test for Hepatitis C virus indicating acute or chronic infection.

4) Allergies and Adverse Drug Reaction

a) History of severe hypersensitivity reactions to other monoclonal antibodies

b) History of allergy or hypersensitivity to study drug components

5) Other Exclusion Criteria

a) Prisoners or 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 (e.g., 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 does not permit the re-enrollment of a participant that has discontinued the study as a pre-treatment failure.

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 allocation.

Study treatment includes only Investigational [Medicinal] Product (IP/IMP).

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 CA209870					
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	100 mg (10 mg/mL and 40 mg/4 mL)	IP	Open Label	Clear to opalescent colorless to pale yellow liquid. May contain particles 240 mg kit contains: 2 x 100 mg vials (10 mL/vial) and 1 x 40 mg vial (4 mL/vial) or carton containing 5 vials of 100 mg	2° to 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	Q2 weeks	IV

7.2 Method of Treatment Assignment

All participants will be assigned to treatment using an Interactive Response Technology (IRT). Users 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

This is an open-label, single arm study and blinding procedures are not applicable.

7.4 Dosage Modification

7.4.1 Nivolumab Dosing

Participants should begin study treatment within 3 calendar days of treatment assignment. Participants should receive nivolumab at a dose of 240 mg as a 30 minute infusion on Day 1 of each treatment cycle until progression, unacceptable toxicity, withdrawal of consent, or study end, whichever occurs first. Nivolumab treatment will be given up to 24 months in the absence of disease progression or unacceptable toxicity. Treatment with nivolumab could be reinitiated as per the initial schedule for subsequent disease progression and administered for up to 1 additional year.

Premedications are not recommended for the first dose of nivolumab. Participants should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.4.5 and Section 8.1.

There will be no dose escalations or reductions of nivolumab allowed. Participants may be dosed within a ± 3-day window and no less than 12 days from the previous dose during q2w cycles.

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

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) and 40 mg/mL (10 mg/mL): nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding in-line filter at the protocol-specified doses. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 1 mg/mL. Instructions for dilution and infusion of nivolumab injection may be provided in the clinical protocol, pharmacy binder, or pharmacy reference sheet. Care

must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

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

7.4.2 Dose Delay Criteria for Nivolumab

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

Nivolumab administration should be delayed for the following:

- Grade 2 non-skin, drug-related adverse event, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities
- Grade 3 skin, drug-related adverse event
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
    - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay
- Dose delay for changes in AST or ALT as follows:
    - If a subject has a baseline AST or ALT that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity (2 grade shift)
    - If a subject has baseline AST or ALT within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity (2 grade shift)
    - If a subject has baseline AST or ALT within the Grade 2 toxicity range, delay dosing for a two-fold drug-related increase in AST or ALT or for AST or ALT values 8 x ULN (whichever is lower).
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

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

7.4.3 Criteria to Resume Treatment

Participants may resume treatment with study drug when the drug-related AE(s) resolve 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
- For participants with Grade 2 AST, ALT, or TBILI elevations, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.

- Participants with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 8) 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 BMS Medical Monitor.

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

7.4.4 Nivolumab Treatment beyond Disease Progression

Accumulating evidence indicates a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[34] Participants treated with nivolumab will be permitted to continue nivolumab treatment beyond initial study criteria defined PD or other hematologic criteria, assessed by the investigator, as long as they meet the following criteria:

- Investigator-assessed clinical benefit without rapid disease progression
- 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)
- Participants 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.

The decision to continue treatment beyond initial progression should be discussed with the BMS Medical Monitor and documented in the study records.

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 PD. 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 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 PD. This includes an increase in the sum of diameters of all target lesions and/ or the diameters of new measurable lesions compared to the time of initial PD. Nivolumab 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.

7.4.5 Treatment of Nivolumab Related Infusion Reactions

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

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

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

- Remain at bedside and monitor 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 administration.

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

- Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the 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 nivolumab will be not be administered at that visit.
- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before nivolumab infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

For Grade 3 or 4 symptoms: (severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms

following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates). Grade 4: Life-threatening; pressor or ventilatory support indicated):

- Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline and treat the 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. Study drug 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).

7.4.6 Protocol-Specific Recommendations for Management of Hepatic Events

The nivolumab program has developed a standardized approach for the management of hepatic events based on cumulative data across the program in subjects with normal hepatic function. Across most nivolumab studies, the eligibility criteria for inclusion are based on a maximum AST or ALT < 3 x ULN; therefore, only subjects with normal to grade 1 LFTs have been enrolled.

For CA209870, the upper limits for inclusion were therefore adjusted to account for baseline liver dysfunction. Subjects with AST or ALT elevations within the CTCAE Grade 2 range are eligible for inclusion. In contrast, the majority of subjects included in prior nivolumab studies have had no higher than a CTCAE grade 1 AST or ALT elevation. Criteria for dose delay, resumption, and discontinuation are in Section 7.4.2, Section 7.4.3, and Section 8.1, respectively. The protocol-specific approach for the management of hepatic events is as follows:

- If AST or ALT levels do not improve with a dose delay of 3-5 days or if the levels worsen, initiate steroid therapy at 0.5-2 mg/kg/day methylprednisolone or oral equivalent.
- For ALT or AST levels > 8x ULN, initiate steroid therapy promptly at 1-2 mg/kg/day methylprednisolone or oral equivalent.
- For all subjects initiating steroids, consult the BMS Medical Monitor within 24 hours after initiation of steroids. Gastroenterology consult is recommended.
- If AST or ALT levels do not improve within 3-5 days or the levels worsen after the start of steroid therapy, discuss with the BMS Medical Monitor the possibility of adding mycophenolate mofetil at 1 g BID.
- Tapering of steroids can start once AST or ALT levels have declined by 1 CTCAE grade. Taper steroids slowly over no less than 1 month.

As outlined in Section 7.4.3, nivolumab therapy may resume when AST or ALT have returned to near baseline unless the criteria for permanent discontinuation are reached (Section8.1).

7.4.7 Management Algorithms for Immuno-Oncology Agents

Immuno-oncology (I-O) agents, such as nivolumab are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. 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

Treatment management algorithms are found in the BMS-936558 (nivolumab) Investigator Brochure.[33]

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

Further guidance and information for final disposition of unused study treatment are provided in CA209870 Study Reference Manual.

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 and during nivolumab treatment are described below. Medications taken within 2 weeks prior to study drug administration and medications taken during study must be recorded on the CRF.

1) Prior exposure to nivolumab (BMS-936558)
2) Immunosuppressive agents (except to treat a drug-related adverse event)
3) Immunosuppressive doses of systemic corticosteroids (except as stated in Section 7.7.1.1)
4) Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of cancer)
5) Exposure to any systemic treatment within 2 weeks of nivolumab administration.
6) No concomitant medications (prescription, over-the-counter or herbal) are to be administered during study unless they are prescribed for treatment of specific clinical events. Any concomitant therapies must be recorded on the CRF.

7.7.1.1 Permitted Therapy

Participants are permitted the use of topical, ocular, intra-articular, intranasal and inhalation corticosteroids (with minimal system absorption). Adrenal replacement steroid doses > 10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, for contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted. Prior palliative radiotherapy must have been completed at least 2 weeks prior to first dose.

7.7.1.2 Palliative Local Therapy

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

Participants requiring palliative local therapy should be evaluated for objective evidence of disease progression prior to the initiation of such therapy, particularly if the most recent tumor assessment was more than 4 weeks prior to the start of local therapy. If progression per study

defined response criteria is identified on any tumor assessments prior to the initiation of palliative local therapy, then participants must either discontinue study drug treatment or they must meet criteria to continue treatment beyond progression in order to resume immunotherapy after palliative local therapy.

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

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 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 Imaging Restriction and Precautions

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

7.7.2.2 Surgical Resection Following Initial Response

In some clinical scenarios, investigators may choose to resect solitary lesions in participants with metastatic disease and render the patient free of macroscopic disease. Participants enrolled in this study may have lesions surgically resected only if confirmation of response is documented at least 4 weeks after previous scan and following consultation with the BMS Medical Monitor. If tumor shrinkage of the solitary lesion is noted on the re-staging assessment, it is highly encouraged that surgical resection be delayed until subsequent scans fail to demonstrate further shrinkage.

7.8 Treatment After the End of the Study

At the conclusion of the study, participants who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study treatment. Study treatment will be provided via an

extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of BMS.

BMS reserves the right to terminate access to BMS supplied study treatment if any of the following occur: a) the study is terminated due to safety concerns; b) the development of the nivolumab 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. d) therapeutic alternatives become available in the local market. In all cases BMS will follow local regulations.

8. DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

Participants MUST discontinue investigational product 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 adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the 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.

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 adverse event lasting > 7 days or recurs, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:
    - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
    - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
    - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
        - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
        - Grade ≥ 3 drug-related AST, ALT or total bilirubin requires discontinuation*
        - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2x ULN

*In most cases of Grade 3 AST or ALT elevation, study drug(s) will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants

continuation of study drug(s), a discussion between the investigator and the BMS Medical Monitor/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
    - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis.
    - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
    - Grade 4 drug-related endocrinopathy AEs, such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor.
- Any event that leads to delay in dosing lasting > 6 weeks from the previous dose requires discontinuation, with the following exceptions:
    - Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed. Prior to re-initiating treatment in a participant with a dosing delay lasting > 6 weeks from the previous dose, the BMS Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.
    - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor.

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

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

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 BMS-936558 (nivolumab) Investigator Brochure[33] or if the investigator believes that it is in best interest of the participant.

Refer to the Section 2 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 Schedule of Activities. 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.

8.1.1 Post Study Treatment Study Follow-up

Overall survival is a key endpoint of the study. Post treatment 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.

BMS may request that survival data be collected on all treated/randomized participants outside of the protocol defined window (see Schedule of Activities Table 2.3). At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contacts or is lost to follow-up.

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.

BMS may request the survival data be collected on all treated/randomized participants outside of the protocol defined window (see Table 2-3). At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contacts or is lost to follow-up.

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.
- 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. 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, including non-study required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug induced liver enzyme evaluations) will be monitored during the follow-up phase via on

site/local labs until all study drug related toxicities resolve, return to baseline, or are deemed irreversible.

- If a subject shows pulmonary-related signs (hypoxia, fever) or symptoms (eg. dyspnea, cough, fever) consistent with possible pulmonary adverse events, the subject should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm in the BMS-936558 (nivolumab) Investigator Brochure.[33]
- Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

9.1 Efficacy Assessments

Duration of response and progression-free survival will be evaluated by local investigator using RECIST v1.1.

9.1.1 Imaging Assessment for the Study

The imaging assessment schedule is provided in Table 9.1.1-1.

Table 9.1.1-1: Imaging Assessment Schedule

Study Day	Event Relative to Dosing	Tumor Assessment
Screening	N/A	X
Week 9	N/A	X
Every 8 weeks for 48 weeks	N/A	X
Every 12 weeks after 48 weeks	N/A	X

Note: Screening assessments should be performed within 28 days of treatment.

Study evaluations (tumor assessments) will take place in accordance with the Section 2 Schedule of Activities.

For solid tumors, CT with oral and intravenous contrast or contrast-enhanced MRI are 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 28 days of treatment. Brain MRI without and with contrast 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 the appropriate response criteria should be used when recording data, and should again be used for all subsequent assessments. Bone scan, 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 8 weeks for the first 48 weeks, every 12 weeks thereafter, or sooner if clinically indicated. Radiographic tumor assessments will be conducted until disease progression, lost to follow-up, or withdrawal of study consent. Participants treated beyond progression should continue radiographic tumor assessments until discontinuation of study therapy or start of subsequent therapy as defined in Section 8.1.1 for disease progression.

Tumor assessments for all participants should continue as per protocol even if dosing is interrupted. Tumor assessment should be made by the same investigator or radiologist for each assessment whenever possible. Changes in tumor sizes and tumor responses to guide ongoing study treatment decisions will be assessed by the investigator using appropriate response criteria. (See Section 7.7.2 regarding additional precautions).

Only data for the procedures and assessments specified in this protocol should be submitted to BMS on a case report form. Additional procedures and assessments may be performed as part of standard of care; however, data for these assessments should remain in the participant's medical record and should not be provided to BMS, unless specifically requested. Sites should be trained prior to scanning the first study participant.

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.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

The collection of nonserious AE information should begin at initiation of study treatment for a minimum of 100 days following discontinuation of study treatment and at the timepoints specified in the Schedule of Activities (Section 2). Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the participants.

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the 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 of the last dose of study treatment. For participants assigned to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of treatment assignment.

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 subject. (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

- Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section Appendix 3).
- Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment as appropriate.
- All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic). Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

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

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 (e.g., 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 nonserious AE CRF page or SAE Report Form electronic, as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the 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 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 Immune-mediated Adverse Events

Immune-mediated adverse events (IMAEs) 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 subject's case report form.

9.2.9 Other Safety Considerations

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

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 should:

1) Contact the BMS 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 BMS 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.

9.4.1 Physical Examinations

Refer to Schedule of Activities.

9.4.2 Vital Signs

Refer to Schedule of Activities.

9.4.3 Clinical Safety Laboratory Assessments

Investigators must document their review of each laboratory safety report.

Hematology	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Serum Chemistry	
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Alkaline phosphatase Lactate dehydrogenase (LDH) Blood urea nitrogen (BUN) or serum creatinine level	Calcium Sodium Potassium Chloride Phosphate Glucose
Serology	
Serum for hepatitis B and C testing (HBV sAg and HCV Ab or HCV RNA).	
Serum for HIV testing where locally mandated	
Other Analyses	
Thyroid function testing (including TSH, free T3, and free T4)	

9.4.4 Imaging Safety Assessment

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

9.5 Pharmacokinetic

Not applicable.

9.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.7 Pharmacogenomics

Not applicable.

9.8 Biomarkers

Table 9.8-1: Biomarker Tissue [redacted] Sample Collection

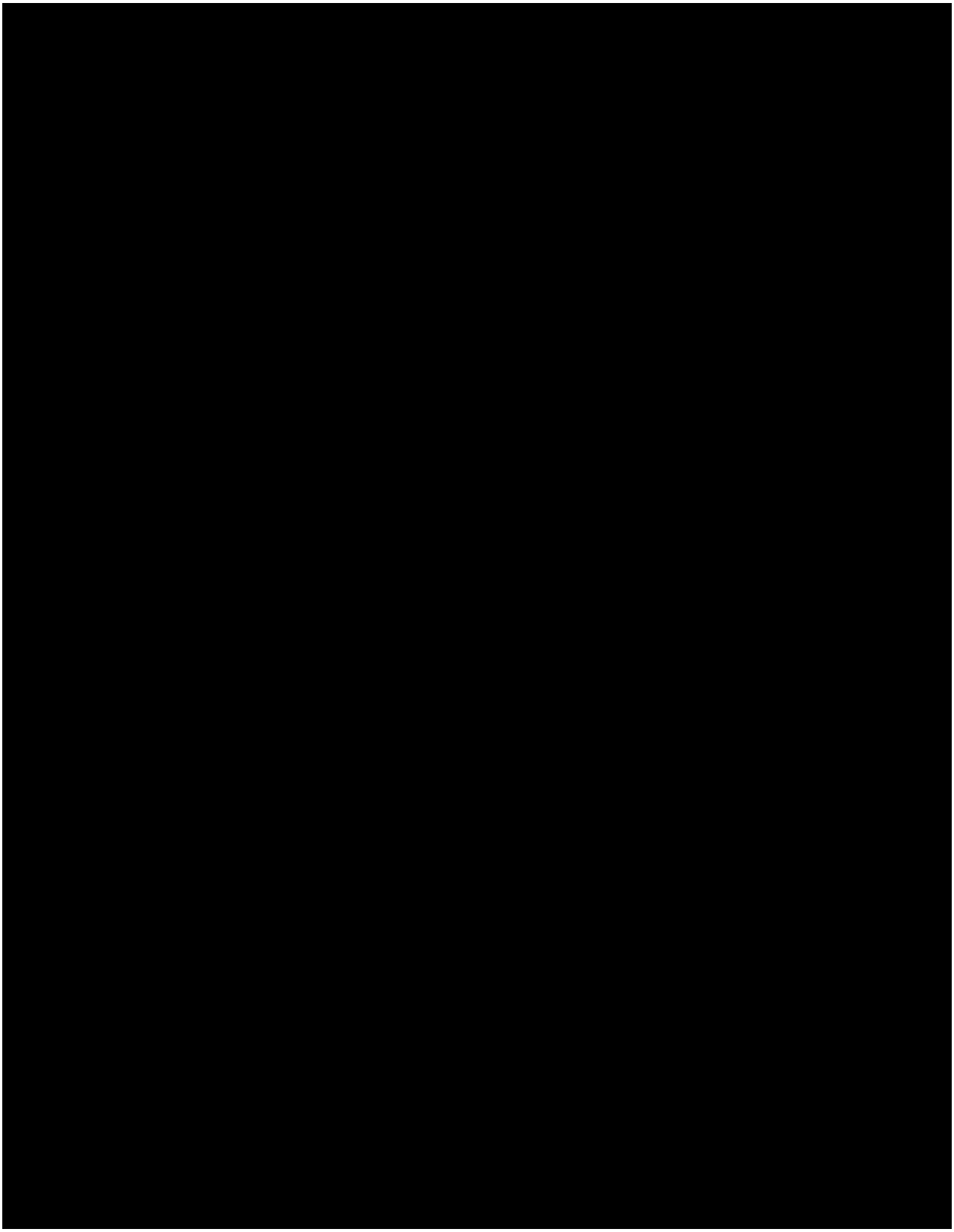
Study Day	Archival Tumor or Fresh Biopsy Tissue	[redacted]
Screening	X	

[redacted]

PD-L1 testing [redacted] testing: Archival or fresh formalin-fixed paraffin-embedded (FFPE) tumor tissue collected within one year (block) or within 6 months (sectioned slide) must be submitted to central laboratory for PD -L1 IHC testing prior to the treatment assignment. All samples will be stained and scored for PD-L1 expression using the PD-L1 IHC 28-8 pharmDx kit (Dako). Stained tissue samples will be assessed by the pathologist who has been trained 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]

All analyses will be completed retrospectively and within the scope of informed consent.



9.10 Patient Reported Outcomes

LCSS (Lung Cancer Symptom Scale) is designed as a site-specific measure of quality of life (QL), particularly for use in clinical trials. It evaluates six major symptoms associated with lung malignancies and their effect on overall symptomatic distress, functional activities, and global QL. It captures in detail those dimensions most likely to be influenced by therapeutic interventions and evaluates other dimensions globally. It consists of two scales: one completed by the patient and an optional one for health care professionals ("counterpart observer") to provide context.[35] LCSS remains popular and has been used in clinical trials for assessing quality of life.[36] It comprises two different scales, one rated by the patient and the other by the physician. The patient scale contains nine items, including three summation and six symptom items. Each item is marked on a VAS of 100 mm length, with zero denoting the lowest rating and 100 the highest. The mean of six main symptoms is used to calculate the 'average symptom burden' of the patient. The physician scale consists of six items pertaining to the main lung cancer symptoms. These are rated as 0, 25, 50, 75, and 100 depending on symptom severity.[37]

EQ-5D is the one of the generic preference-based instruments which are advantageous in that they facilitate calculation of QALYs for subsequent application to cost-utility analysis (CUA) as

well as allow for comparison of HR-QOL across different conditions. EQ-5D is widely used and simple to administer and score. The instrument's descriptive system consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels, reflecting "no health problems," "moderate health problems," and "extreme health problems." A dimension for which there are no problems is said to be at level 1, while a dimension for which there are extreme problems is said to be at level 3.[38] Thus, the vectors 11111 and 33333 represent the best health state and the worst health state, respectively, described by the EQ-5D. Altogether, the instrument describes 35 = 243 health states. Empirically derived weights can be applied to an individual's responses to the EQ-5D descriptive system to generate an index measuring the value to society of his or her current health. Such preference-weighting systems have been developed for Japan, UK, US, Spain, Germany, and even in China. In addition, the EQ-5D includes a visual analog scale that allows respondents to rate their own current health on a 101-point scale ranging from "best imaginable" to "worst imaginable" health.

In addition to the aforementioned patient-reported outcomes [redacted] will be collected for all participants using an internal case report form. The CRF will record information about hospital admissions, including number of days spent in various wards, discharge diagnosis, and medical services item and cost received while inpatient, as well as outpatient visits related to lung cancer therapy, including date of visit, reason for visit, type of visit and medical services item and cost. [redacted]

Table 9.10-1: Timepoints and Windows for EORTC-QLQ-C30 and EuroQoL EQ-5D Assessments

Nominal Timepoint	Time Window
Baseline	3 days of C1D1 dosing and prior to any study procedures
Every 4 Weeks for 6 months	Every 4 weeks (within 5 days of C1D1) for 6 months
Every 6 Weeks	Every 6 weeks (within 5 days of C1D1) for remainder of study
Follow-Up 1	If assessment is post last dose and within 76 days of last dose (if date of discontinuation is within 35 day after last dose) If assessment is post last dose and within 40 days of date of discontinuation (if date of discontinuation is greater than 35 days after last dose)
Follow-Up 2	If assessment is post 76 days of last dose(if date of discontinuation is within 35 day after last dose) If assessment is post 40 days of date of discontinuation (if date of discontinuation is greater than 35 days after last dose)

10. STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

The incidence rate of treatment related select high grade AE is 0.5-3% of nivolumab 3mg/kg every two weeks with infusion time no less than 30 minutes based on the Checkmate 153 study which published in ASCO 2016,[39] and 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, so we assume that the incidence rate of treatment related select high grade AE is similar in both 3 mg/kg every 2 weeks and 240mg every 2 weeks.

In order to further characterize the frequency and outcome of the rather infrequent treatment related select adverse of high grade (Grade 3-5), the current study will treat approximately 400 participants (assuming 340 non-HBV infected participants and 60 HBV infected participants) with nivolumab. The 95% confidence intervals of the incidence rate of high grade (grade 3-5) treatment related select adverse events were listed as below table. With the screen failure rate of 15%, totally 470 participants will be screened.

Table 10.1-1 shows the CI using Clopper Pearson methods for a sample size of 340 non-HBV infected participants and all treated participants.

Table 10.1-1: 95% Confidence Intervals of Adverse Event Rate

AE Incidence Rate	Non-HBV (340 participants)	Overall (400 participants)
0.5%	0.07%, 2.11%	0.06%, 1.79%
1%	0.32%, 2.98%	0.27%, 2.54%
3%	1.63%, 5.71%	1.56%,5.18%

10.2 Populations for Analyses

The following defined population will apply to pooled tumor types and individual tumor histology and molecular genotype, unless otherwise specified:

Population	Description
Enrolled participants	All participants who signed an informed consent form and were registered into the IRT.
Treated participants	All enrolled participants who received at least one dose of study drug.
All response evaluable participants	All treated participants who have baseline and at least one on-study evaluable tumor measurement.
Non-HBV infected participants	All treated participants with HBVsAg negative by serum testing.
HBV infected participants	All treated participants with HBVsAg positive by serum testing.
Biomarker participants	All treated participants with available tissue/blood samples.

10.3 Statistical Analyses

Statistical analyses will be performed for pooled for each histology and molecular genotype type unless otherwise specified.

Demographic and baseline laboratory results will be summarized using descriptive statistics for all treated participants. Baseline characteristics, including demographics (age, gender, geographic location, race/ethnicity) and clinical characteristics (date of diagnosis, disease stage, liver function status, performance status, co-morbidity/prognostic indicators, location of metastases) will be collected at the time of treatment initiation for each cohort. General descriptive statistics, including mean and standard deviation (SD) for continuous variables, count and percentage for categorical variables will be used extensively to examine these variables.

The statistical analysis plan will be developed and finalized before database lock, will describe all planned analyses, and procedures for accounting for missing, unused, and spurious data. A summary of planned statistical analyses of the primary and secondary endpoints is in Section 10.3.1 and Section 10.3.2.

10.3.1 Efficacy Analyses

Endpoint Definition	**Statistical Analysis Methods**
Primary	
Not applicable	
Secondary	
Overall Survival (OS) is defined as the time from the first dosing date to the date of death. Participants without documentation of death will be censored on the last date the participant was known to be alive.	Time to event distribution will be estimated using Kaplan Meier techniques. Median OS along with 95% CI will be constructed based on a log-log transformed CI for the survivor function. OS Rates at fixed timepoints (6, 12, 18, and 24 months) will be derived from the Kaplan Meier estimate and corresponding confidence interval will be derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survivor function.
Time to Treatment Failure (TTF) is defined as the minimum of the time from treatment assignment to disease progression (determined by investigator assessments using RECIST 1.1), death or last dose date if a subject progressed, died or discontinued from treatment for any reasons other than "maximum clinical benefit" and	Time to event distribution will be estimated using Kaplan Meier techniques. Median TTF along with 95% CI will be constructed based on a log-log transformed CI for the survivor function. Sensitivity analysis will be conducted to censor TTF for discontinuations due to patient

Endpoint Definition	Statistical Analysis Methods
"administrative reasons by sponsor". TTF is censored at the last dose date for subjects who continued on treatment without progression (per RECIST 1.1) or death at the time of the database lock.	preference.
Progression-Free Survival (PFS) is defined as the time from first dose date to the date of the first documented tumor progression (per RECIST 1.1) or death due to any cause. Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on study tumor assessments and did not die will be censored on their first dose date. Subjects who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last evaluable tumor assessment prior to initiation of the subsequent anti-cancer therapy.	Time to event distribution will be estimated using Kaplan Meier techniques. Median PFS along with 95% CI will be constructed based on a log-log transformed CI for the survivor function.
Objective Response Rate (ORR) is defined as the proportion of all treated subjects whose best overall response (BOR) from baseline is either a CR or PR per RECIST 1.1 criteria. BOR is determined by the best response designation recorded between the first dose date and the date of objectively documented progression or the date of subsequent anti-cancer therapy, whichever occurs first. For subjects without documented progression or subsequent anti-cancer therapy, all available response designations will contribute to the BOR determination. For subjects who continue nivolumab beyond progression, the BOR should be determined based on response designations recorded at the time of the	ORR will be summarized by binomial response rates and their corresponding two-sided 95% exact CIs using Clopper-Pearson method.

Endpoint Definition	Statistical Analysis Methods
initial RECIST 1.1 defined progression.	
Duration of 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. Subjects who neither progress nor die will be censored on the date of their last assessment. The censoring algorithm for DOR will be the same as used for PFS definition. This endpoint will only be evaluated for participants with BOR of CR or PR.	The DOR will be summarized for all treated participants who achieve confirmed PR or CR using the Kaplan-Meier (KM) product-limit method. Median values of DOR, along with two-sided 95% CI using Brookmeyer and Crowley method, will also be calculated.
[redacted]	

10.3.1.1 Efficacy Analysis in Subgroups:

The efficacy analyses methods for OS, TTF, PFS, ORR, and DOR will also be evaluated in different subgroups, including squamous and non-squamous subgroups, PD-L1 positive and PD-L1 negative protein expression subgroups, non-HBV infected and HBV infected subgroups, and EGFR mutation, ALK positive and WT subgroups. The analyses methods described above for OS, ORR, and PFS will be repeated for each of the subgroup.

10.3.2 Safety Analyses

Endpoint Definition	Statistical Analysis Methods
Primary and Secondary	
Safety and tolerability	Descriptive statistics of safety will be presented using NCI CTCAE version 4. All on-study AEs and SAEs and drug-related AEs and SAEs will be tabulated using worst grade per NCI CTCAE v.4 criteria by system organ class and MedDRA preferred term. On-study lab parameters including hematology, chemistry, liver function, thyroid function, and renal function will be summarized using worst grade per NCI CTCAE v.4 criteria.

10.3.3 Other Analyses

Exploratory analyses for [redacted] health outcomes [redacted] will be described in the statistical analysis plans finalized before database lock. These analyses will be presented separately from the main clinical study report.

10.3.3.1 Patient Reported Outcomes

The LCSS and EQ-5D completion rates, defined as the proportion of questionnaires actually received out of the expected number will be calculated and summarized at each assessment point. The EQ-5D (with two essential components: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS) will be used to assess the subject's overall health status. Proportion of subjects reporting problems for the 5 EQ-5D dimensions at each assessment time point will be summarized by level of problem. Percentages will be based on number of subjects assessed at assessment time point. Value set for Chinese population37 will be used to get utility values for each individual. The baseline and change from baseline of the EQ-5D and LCSS scores at each assessment point will be summarized using descriptive statistics. The disease-related symptom deterioration rate at week 12 and week 24 as measured by LCSS and its corresponding 95% CI will also be calculated by Clopper-Pearson method. All summaries for LCSS and EQ-5D will be done for all treated participants, and also by tumor histology (SQ or NSQ), by PD-L1 expression (PD-L1 negative or PD-L1 positive), by infection status (HBV infection or non-HBV infection), and by molecular type (EGFR mutation, ALK translocation, or WT).

10.3.4 Interim Analyses

Not applicable.

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AT	aminotransaminases
BMS	Bristol-Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
C	Celsius
Ca	calcium
CBC	complete blood count
CBR	clinical benefit rate
CFR	Code of Federal Regulations
CI	confidence interval
$C1^-$	chloride
CLcr	creatinine clearance
CRF	case report form, paper or electronic
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
dL	deciliter
DMC	Data monitoring committee
[redacted]	[redacted]
DNA	Deoxynucleic acid
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EORTC	European Organization for Research and Treatment of Cancer
eg	exempli gratia (for example)
FDG	fluorodeoxyglucose
FSH	follicle stimulating hormone

Term	Definition
GCP	Good Clinical Practice
[redacted]	[redacted]
GFR	glomerular filtration rate
h	hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCO_3^-	bicarbonate
HIV	human immunodeficiency virus
HR	heart rate
ICH	International Conference on Harmonisation
IHC	immunohistochemistry
ie	id est (that is)
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
IRB	Institutional Review Board
IRC	Independent Review Committee
IRT	Interactive Response Technology
IU	International Unit
IV	intravenous
K^+	potassium
kg	kilogram
L	liter
LDH	lactate dehydrogenase
mg	milligram
Mg^{++}	magnesium
min	minute
mL	milliliter

Term	Definition
MRI	magnetic resonance imaging
N	number of subjects or observations
Na	sodium
N/A	not applicable
NCI	National Cancer Institute
NIMP	non-investigational medicinal products
ORR	objective response rate
OS	overall survival
PD	pharmacodynamics
PET	positron emission tomography
PFS	progression free survival
PK	pharmacokinetics
QOL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
RBC	red blood cell
SAE	serious adverse event
SD	standard deviation
SOP	Standard Operating Procedures
t	temperature
T	time
TSH	thyroid stimulating hormone
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
WNOCBP	women **not** of childbearing potential

APPENDIX 2 STUDY GOVERNANCE 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 (e.g., advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

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

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

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 • nonstudy disposition (e.g., lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study drug integrity in accordance with

If	Then
	requirements applicable under law and the SOPs/standards of the sourcing pharmacy. These records should include: • label identification number or batch number • amount dispensed to and returned by each 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.

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

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

The completed CRF, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. Subinvestigators in Japan may not be delegated the CRF approval task 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 (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., 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 (e.g., cytotoxics or biologics).

	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, i.e., incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

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:

- External Principal Investigator designated at protocol development

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

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: o 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) o elective surgery, planned prior to signing consent o admissions as per protocol for a planned medical/surgical procedure o routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy) o medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases o 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) o 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.)

Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study treatment is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 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 causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following:

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

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

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

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 drug or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

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

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

REPORTING OF SAES TO SPONSOR OR DESIGNEE

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

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

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

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.

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

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

Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b] • Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and intrauterine hormone-releasing system (IUS)[c] • Intrauterine device (IUD)[c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. [c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

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

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

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

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

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

COLLECTION OF PREGNANCY INFORMATION

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 PERFORMANCE STATUS

1 ECOG PERFORMANCE STATUS

Table 1: ECOG Performance Status

Grade	ECOG
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, e.g., 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

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

APPENDIX 6 RECIST 1.1 GUIDELINES

1 EVALUATION OF LESIONS

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

1.1 Measurable

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

1. 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
2. 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
3. 20 mm by chest x-ray

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

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

1.2 Non-Measurable

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

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

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should

be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

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

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

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

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.

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 (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 and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10mm short axis).

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

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

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

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 a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

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.

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

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

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

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

2.3.2 Time Point Response

It is assumed that 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

Table 2.3.2-1: Time Point Response: Patients With Target (+/- Non-Target) Disease			
Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**
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 later. In this circumstance, the best overall response can be interpreted as in Table 2.3.3-1.

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

Table 2.3.3-1: Best Overall Response (Confirmation of CR&PR Required)		
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**BEST Overall Response**
CR	CR	CR
CR	PR	SD, PD OR PR[a]
CR	SD	SD provided minimum criteria for SD duration[b] met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration[b] met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration[b] met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration[b] met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration [b]met, otherwise, NE
NE	NE	NE
CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable		

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

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

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 repeat assessments that should be performed no less than 28 days after the criteria for response are first met. For this study, the next scheduled tumor assessment can meet this requirement.

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