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)

NCT Number: NCT03195491

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STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

AN OPEN LABEL, SAFETY STUDY OF PARTICIPANTS WITH NON-SMALL CELL LUNG CANCER RECEIVING SECOND-LINE NIVOLUMAB MONOTHERAPY IN ASIA
PROTOCOL CA209870

VERSION Final # 1.0

[redacted] APPROVAL SIGNATURES

Study Title: AN OPEN LABEL, SAFETY STUDY OF PARTICIPANTS WITH NON-SMALL CELL LUNG CANCER RECEIVING SECOND-LINE NIVOLUMAB MONOTHERAPY IN ASIA
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Protocol Date: Revised Protocol 02 – 25 October 2017

[redacted]

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Date

[redacted]

[redacted]

Bristol-Myers Squibb APPROVAL SIGNATURES

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Protocol Date: **Revised Protocol 02 – 25 October 2017**

Reviewed at Bristol-Myers Squibb by:

[redacted]

05/16/2018

Date

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LIST OF ABBREVIATIONS

2L	second line
AE	adverse event(s)
AEOSI	Other events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ASBI	Average Symptom Burden Index
AST	aspartate aminotransferase
BMI	body mass index
BMS	Bristol-Myers Squibb
BOR	Best overall response
BP	Blood Pressure
BUN	blood urea nitrogen
CI	confidence interval
CR	complete response
CRF	Case report form
CSR	clinical study report
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DNA	Deoxynucleic acid
DOR	Duration of Response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	estimated glomerular filtration rate
EQ-5D	EuroQoL Five Dimensions Questionnaire
[redacted]	[redacted]
[redacted]	[redacted]
HB	hemoglobin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
[redacted]	[redacted]
HIV	Human Immunodeficiency Virus
HR	heart rate
ICH	International Conference on Harmonization
IHC	immunohistochemistry
IMAEs	Immune-mediated AEs
IRT	Interactive Response Technology

IV	intravenous
IWRS	interactive web response system
LCSS	Lung Cancer Symptom Scale
LDH	lactate dehydrogenase
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NSCLC	Non-small Cell Lung Cancer
NSQ	non-squamous
PD	progressive disease
PFS	Progression-Free Survival
PK	pharmacokinetics
PPK	population pharmacokinetic
PR	partial response
PR interval	electrocardiographic interval occurring between the onset of the P wave and the QRS complex, representing time for atrial and ventricular depolarization, respectively
PRO	Patient Reported Outcomes
PS	Performance status
PT	Preferred Term
ORR	Objective Response Rate
OS	Overall Survival
Q2W	every 2 weeks
QoL	Quality of Life
QRS	electrocardiographic deflection between the beginning of the Q wave and termination of the S wave, representing the time for ventricular depolarization
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur
QTcF	QT interval corrected by Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RR	interval between successive heart beats using the R-wave peaks
SAE	serious adverse event(s)
SAP	statistical analysis plan
SAS	Statistical Analysis System software
SD	stable disease
SI	standard international unit
SOC	System Organ Class
SQ	squamous
TC	total cholesterol
TKI	tyrosine kinase inhibitor

TSH	thyroid stimulating hormone
TTF	Time to Treatment Failure
ULN	upper limit of normal
US	United States
VAS	Visual Analogue Scale
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential

1 BACKGROUND AND 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.

The purpose of this document is to provide details about the statistical analysis methods for the study an open label, safety study of participants with non-small cell lung cancer receiving second-line nivolumab monotherapy in Asia protocol CA209870.

Research Hypothesis:

There is no formal hypothesis to test in this study. 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.

2 STUDY DESCRIPTION

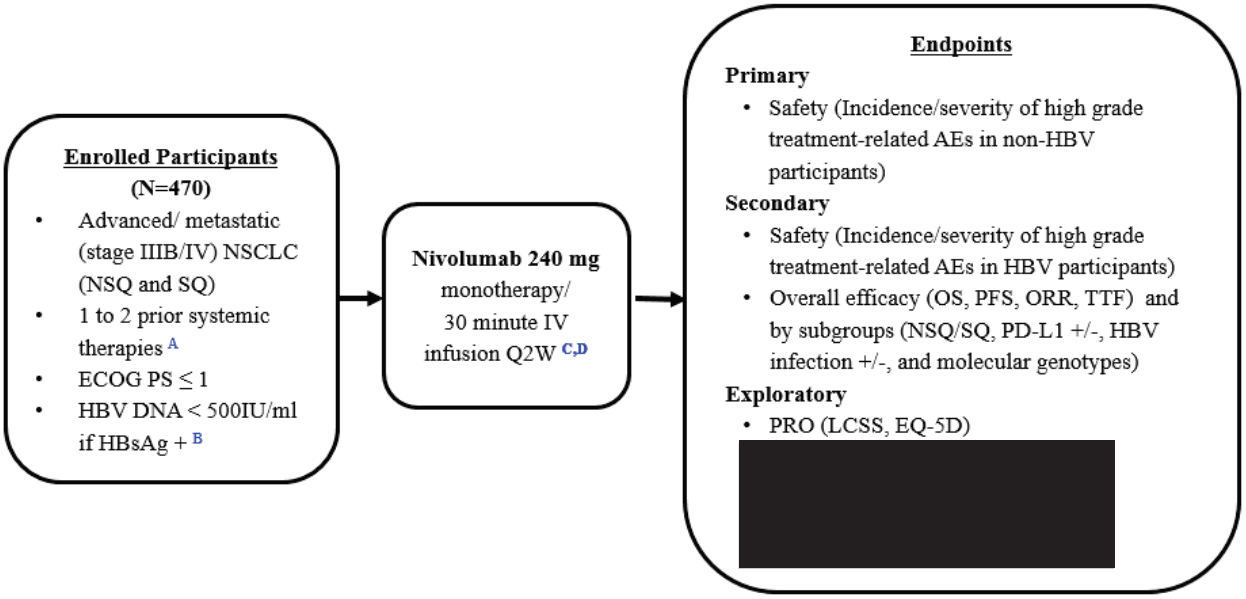
2.1 Study Design

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 Protocol. 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 Appendix 1 Schedule of Activities.

The study design schematic is presented in Figure 2.1.

Figure 2.1: 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 until death or the conclusion of the study.

2.2 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 (Appendix 1).

2.3 Blinding and Unblinding

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

2.4 Protocol Amendments

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-years 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	20-Nov-2016	Not Applicable

2.5 Data Monitoring Committee and Other External Committees

A Data Monitoring Committee (DMC) will not be used for this study.

3 OBJECTIVES

Specific objectives relevant to the study are described within this SAP are described below.

3.1 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.

3.2 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
- To assess safety and tolerability in all participants
- 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

3.3 Exploratory

- To assess overall health status and health utility

[redacted]

4 ENDPOINTS

4.1 Primary

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.

4.2 Secondary

- Incidence and severity of all high grade (combined CTCAE v4 Grade 3-4 and Grade 5) treatment-related select adverse events in HBV participants
- Incidence and severity of AEs and specific laboratory abnormalities in all treated subjects
- 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).

4.3 Exploratory

- The 3-level version of the EQ-5D (EQ-5D-3L) visual analog scale (VAS) and utility index, respectively
- 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]

5 SAMPLE SIZE AND POWER

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[5], 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 5.1 shows the CI using Clopper Pearson methods for a sample size of 340 non-HBV infected participants and all treated participants.

Table 5.1: 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%

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

See Core Safety SAP.

6.2 Treatment Regimens

All subjects will be treated with nivolumab.

Table 6.1 shows selection and timing of dose.

Table 6.1: 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

6.3 Populations for Analyses

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

- **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.
- **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 [redacted] samples.

7 STATISTICAL ANALYSES

Statistical analyses will be performed for all treated participants by HBV status and pooled 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.

7.1 General Methods

Unless otherwise noted, the following subsections describe tabulations of discrete variables, by the frequency and proportion of subjects falling into each category by HBV status and pooled. Percentages given in these tables will be rounded and, therefore, may not always sum to 100%. Percentages less than 0.1 will be indicated as '<0.1'. Continuous variables will be summarized by HBV status and pooled using the mean, standard deviation, median, minimum and maximum values.

Time to event distribution will be estimated using Kaplan Meier techniques. This will be done for overall survival, time to treatment failure, progression-free survival and duration of response. Median survival time along with 95% CI will be constructed based on a log-log transformed CI for the survivor function S(t). Rates at fixed time points 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 S(t).

Since CA209870 is a single arm study, analyses by HBV status will consist of three groups ("Non-HBV", "HBV" and "Total") unless otherwise specified. [redacted]

The conventions to be used for imputing partial dates for analyses requiring dates are described in Section 8.

7.2 Study Conduct

Unless otherwise specified, the study conduct data will be presented on all treated participants by HBV status and pooled.

7.2.1 Relevant Protocol Deviations

The relevant protocol deviations will be summarized, by HBV status and pooled. The following programmable deviations from inclusion and exclusion criteria will be considered as relevant protocol deviations. Non-programmable relevant eligibility and on-treatment protocol deviations, as well as significant (both programmable and non-programmable) eligibility and on-treatment protocol deviations will be reported through [redacted].

At Entrance:

- Participants without histologically- or cytologically-documented NSCLC (SQ or NSQ) who present with Stage IIIB/Stage IV disease.
- Participants without recurrent or progressive disease following multimodal therapy (radiation therapy, surgical resection, or definitive chemo-radiotherapy for locally advanced disease).
- Participants who didn't receive at least 1 to 2 prior systemic therapies.
- Participants with baseline ECOG PS>1.
- Participants with HBV DNA≥500 IU/ml if $HBsAg^{+}$.
- Participants without measurable disease at baseline by CT or MRI 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.

On-study:

- Participants receiving prohibited and/or restricted treatments.

A by-subject listing will be provided.

7.3 Study Population

Unless otherwise specified, the study population data will be presented on all treated participants by HBV status and pooled.

A pre-treatment and end of treatment disposition tables will be summarized using all enrolled participants and all treated participants respectively. The efficacy endpoints such as overall

survival (OS), Best Overall Response (BOR), Objective Response Rate (ORR), Time to Treatment Failure (TTF) and Progression-Free Survival (PFS) will be summarized using all treated participants by HBV status and pooled. The duration of Response (DOR) and duration of SD will be summarized based on all response evaluable participants.

Safety analysis will be based on all treated participants by HBV status and pooled. All the biomarker data will be analyzed based on all biomarker participants by HBV status and pooled.

7.3.1 Subject Disposition

The total number of subjects enrolled (treated or not) will be presented along with the reason for not being treated. This summary will be presented on all enrolled participants pooled together.

Number of subjects who discontinued treatment along with corresponding reason will also be tabulated.

In addition, the below summary will be provided.

- **Pre-Treatment Status:** The total number of subjects entered into the treatment phase and not entering the treatment phase will be presented along with the primary reason for all enrolled participants.
- **Subject Status - End of Treatment:** Subject continuing in the treatment period of this study and primary reason for not continuing in the treatment period will be presented for all treated participants.

Also, total number of subjects by country and investigational site will be provided.

A by subject listing of pre-treatment, end of study and end of treatment status will be provided separately.

7.3.2 Demographics and Baseline Characteristics

Descriptive statistics of the following baseline characteristics will be summarized by HBV status and pooled for all treated participants.

- Age
- Gender
- Race
- Baseline Eastern Cooperative Oncology Group (ECOG) performance status
- Tobacco Use
    - Type of Tobacco
    - Tobacco Use Status
    - Number Per Day
    - Number of Years
- Electronic Cigarette Use

- Initial Disease Diagnosis
    - Time from initial diagnosis to study treatment first dose
    - Disease Stage at Initial Diagnosis
    - Cell type
    - Histological Grade
- Current Disease Diagnosis
    - Time from diagnosis to study treatment first dose
    - Disease Stage at Study Entry: Stage IIIB/IV/Recurrent
    - Subtype of Disease
- Target Lesions at screening
    - Lesion Type
    - Organ Code
    - Procedure Code
    - Measurement
- Non-Target Lesions at Screening
    - Lesion Type
    - Organ Code
    - Procedure Code
- Pulse Oximetry
- Laboratory Test Results HIV
- Laboratory Test Results HBV DNA
- Laboratory Test Results HCV and HBV

A by subject listing will be provided separately for all the above mentioned variables.

7.3.3 Physical Measurements

Descriptive statistics of the following physical measurements will be summarized by HBV status and pooled for all treated participants for each time-point.

- Height (cm)
- Weight (kg)
- BMI (kg/m2)
- ECOG Performance Status

A by-subject listing will be provided.

7.3.4 Medical History

General medical history and disease specific history will be listed by subject.

7.3.5 Prior Therapy

Descriptive statistics of prior therapies will be summarized by HBV status and pooled for all treated participants.

- Prior Surgery Related to Cancer
  - Subjects with surgery (yes/no)
  - Type of Surgery
  - Time from last surgery to study treatment first dose
- Prior Radiotherapy
  - Subjects with radiotherapy (yes/no)
  - Site of Radiotherapy
  - Time from last therapy stop to study treatment first dose
- Prior Systemic Cancer Therapy
  - Subjects with systemic cancer therapy (yes/no)
  - Number of regimens for each subject
  - Setting of regimen (adjuvant therapy/metastatic disease/neo-adjuvant therapy)
  - Line of Therapy (First Line/second line/third line/not applicable/unknown)
  - Best response to regimen (CR/PR/SD/PD/unable to determine/not applicable) - The last response will be considered as best response to regimen in case of multiple records per subject.
  - Time from last therapy stop to study treatment first dose

A by-subject listing will be provided separately for prior surgery related to cancer, prior radiotherapy and prior systemic cancer therapy.

7.3.6 Subsequent Therapy

A by-subject listing will be provided separately for subsequent systemic cancer therapy, on-treatment/subsequent radiotherapy and subsequent surgery.

7.3.7 Physical Examination

Subjects with abnormal baseline physical examination will be tabulated by examination criteria by HBV status and pooled for all treated participants.

The number and percentage of patients reporting physical examination results (Normal/Abnormal)) will be presented per body system for all treated participants. In addition, shift table will be provided.

A by-subject listing will be provided.

7.3.8 Clinical Complaints

Clinical complaints collected at screening will be summarized using count and percentage by CTC grade for all enrolled participants.

A by-subject listing will be provided.

7.3.9 Diagnostic and Medical Treatment Procedures

A by-subject listing will be provided separately for diagnostic and medical treatment procedures.

7.3.10 Previous and Concomitant Prophylactic Vaccinations

A by-subject listing will be provided separately for previous and concomitant prophylactic vaccinations.

7.4 Extent of Exposure

Unless otherwise specified, the exposure data will be presented on treated participants by HBV status and pooled.

7.4.1 Administration of Study Therapy

The following parameters will be summarized (descriptive statistics):

- Relative dose intensity (%) using the following categories: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%.
- Number of doses received (summary statistics)
- Cumulative dose
- Duration of treatment: duration of treatment will be presented using a Kaplan-Meier curve whereby the last dose date will be the event date for subjects who are off study therapy. Subjects who are still on study therapy will be censored on their last dose date. Median duration of treatment and associated 95% CI will be provided.

A by-subject listing of dosing of study medication (record of study medication, infusion details, and dose change) and a listing of batch number will be also provided.

Below table summarizes the key parameters used to calculate dosing data.

Table 7.4-1: Administration of Study Therapy: Definition of Parameters

	Nivolumab
Dosing schedule per protocol	240 mg Q2 weeks
Cumulative Dose	Cumulative dose (mg) is sum of the doses (mg) administered to a subject during the treatment period
Relative dose intensity (%)	[Cumulative dose (mg)/((Last dose date - Start dose date + 14) 240 / 14)] x 100

Table 7.4-1: Administration of Study Therapy: Definition of Parameters

	Nivolumab
Duration of treatment	Last dose date - Start dose date +1

7.4.2 Modifications of Study Therapy

7.4.2.1 Dose Delays

A dose will be considered as actually delayed if the delay is exceeding 3 days (i.e., greater than or equal to 4 days from scheduled dosing date). The length of dose delay is defined as (duration of previous cycle in days - 14). The Dose delays will be divided into following categories: 4 - < 8 days, 8 - < 15 days, 15 - < 43, > 42 days. Reason for dose delay will be retrieved from CRF dosing pages.

The following parameters will be summarized by HBV status and overall:

- Number of dose delayed per subject, Length of Delay, and Reason for Dose Delay
- Number of subjects with at least one dose delayed along with reason for dose delay

7.4.2.2 Dose Modifications

There will be no dose escalations or reductions of nivolumab allowed.

Nivolumab infusion can be interrupted and/or the IV infusion rate can be reduced. This information will be retrieved from CRF dosing pages.

The following parameters will be summarized by HBV status and overall:

- Number of subjects with at least one infusion with IV rate reduced along with the reason of the rate reduction
- Number of subjects with at least one dose infusion interrupted along with the reason for the interruptions and number of infusions interrupted per subject

A by subject listing of study drug administered will be provided. A batch listing number will be also provided.

In addition the following will be summarized:

- Number of subjects with at least one infusion with IV rate reduced along with the reason of the rate reduction
- Number of subjects with at least one dose infusion interrupted along with the reason for the interruptions and number of infusions interrupted per subject

A by subject listing of study drug administered will be provided. A batch listing number will be also provided.

7.4.3 Prior and Concomitant Medications

Prior concomitant medication, defined as medications which are taken before the date of the first dose of study medication.

Concomitant medications, defined as medications other than study medications which are taken at any time on-treatment (i.e. on or after the first day of study therapy and within 100 days following the last dose of study therapy).

Prior and concomitant medications will be coded using the WHO Drug Dictionary. The following summary tables will be provided for all treated participants by HBV status and pooled:

- Prior concomitant medications (subjects with any concomitant medication, subjects by medication class and generic term)
- Concomitant medications (subjects with any concomitant medication, subjects by medication class and generic term)

A by-subject listing will accompany the tables.

7.5 Efficacy

The Overall Survival (OS), Time to Treatment Failure (TTF), Progression-Free Survival (PFS) Objective Response Rate (ORR) and Best Overall Response (BOR) will be summarized using all treated participants by HBV status and pooled. The Duration of Response (DOR) and duration of SD will be summarized based on all response evaluable participants.

7.5.1 Primary Efficacy Analyses

Not applicable.

7.5.2 Secondary Efficacy Analyses

7.5.2.1 Overall Survival (OS)

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 time points (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.

The above methods for OS will be evaluated for pooled analysis and also in the following subgroups:

- Tumor Histology (Squamous and non-squamous)
- Tumor PD-L1 expression level (PD-L1 positive and PD-L1 negative protein expression)

- Infection Status (Non-HBV infected and HBV infected)
- Molecular Type (EGFR mutation, ALK positive and WT).

Overall survival estimate will be graphically displayed for overall and also for each subgroup analysis using the Kaplan-Meier technique.

7.5.2.2 Time to Treatment Failure (TTF)

Time to Treatment Failure (TTF) is defined as the minimum of the time from first dose date 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 "administrative reasons by sponsor".

Clinical progression date is considered as event for time to treatment failure only when treatment is discontinued due to clinical disease progression. For nivolumab subjects treated beyond RECIST 1.1 progression, the event will be at RECIST 1.1 progression date. TTF is censored at the last dose date for subjects who discontinued treatment (without RECIST 1.1 progression) due to maximum clinical benefit or administrative reason 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.

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 preference.

The above methods for TTF will be evaluated for all treated participants by HBV status and pooled. In addition, subgroup analysis will be performed in the following subgroups:

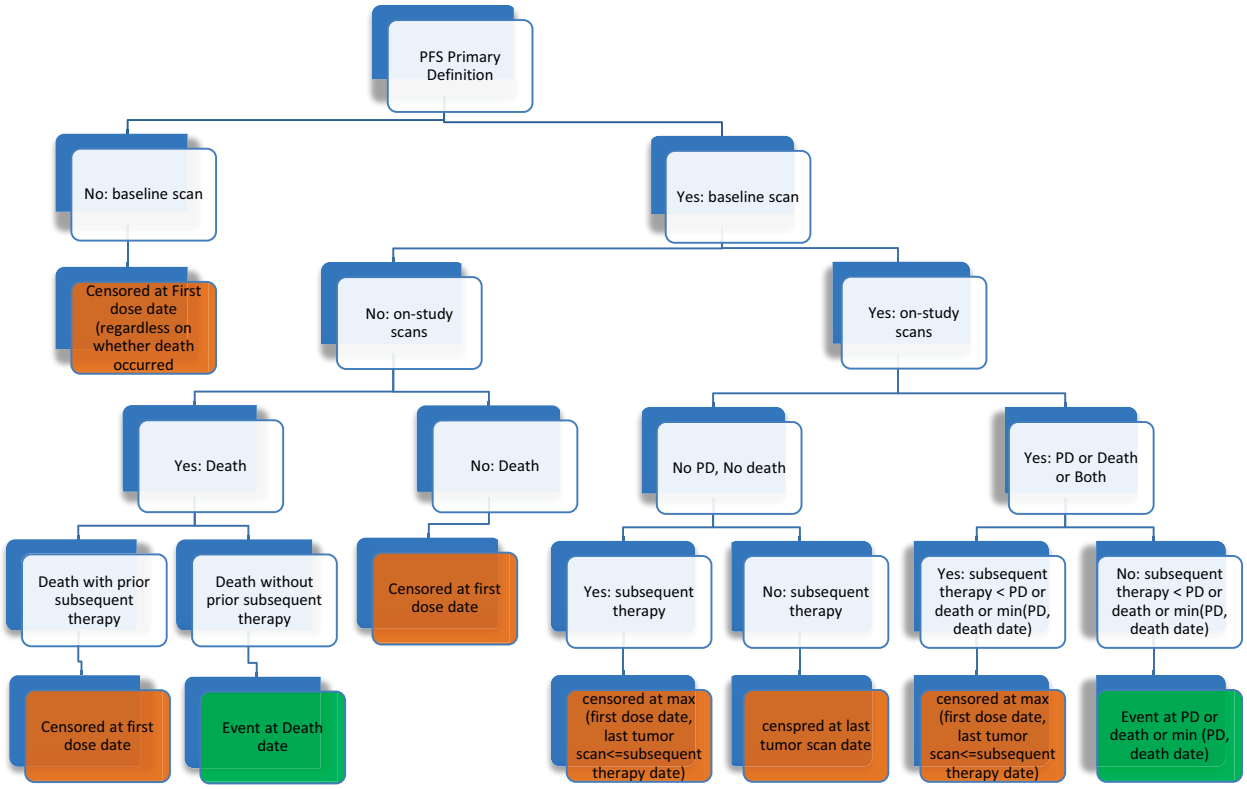
- Tumor Histology (Squamous and non-squamous)
- Tumor PD-L1 expression level (PD-L1 positive and PD-L1 negative protein expression)
- Infection Status (Non-HBV infected and HBV infected)
- Molecular Type (EGFR mutation, ALK positive and WT).

Time to Treatment Failure (TTF) will be graphically displayed for overall and also for each subgroup analysis using the Kaplan-Meier technique.

7.5.2.3 Progression-Free Survival (PFS)

Progression-Free Survival 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.

The above methods for PFS will be evaluated for pooled analysis and also in the following subgroups:

- Tumor Histology (Squamous and non-squamous)
- Tumor PD-L1 expression level (PD-L1 positive and PD-L1 negative protein expression)
- Infection Status (Non-HBV infected and HBV infected)
- Molecular Type (EGFR mutation, ALK positive and WT).

Progression-Free Survival will be graphically displayed for overall and also for each subgroup analysis using the Kaplan-Meier technique.

7.5.2.4 Objective Response Rate (ORR)

Objective Response Rate (ORR) is defined as the proportion of all treated participants 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 initial RECIST 1.1 defined progression.

ORR will be summarized by binomial response rates and their corresponding two-sided 95% exact CIs using Clopper-Pearson method.

The above methods for ORR will be evaluated for pooled analysis and also in the following subgroups:

- Tumor Histology (Squamous and non-squamous)
- Tumor PD-L1 expression level (PD-L1 positive and PD-L1 negative protein expression)
- Infection Status (Non-HBV infected and HBV infected)
- Molecular Type (EGFR mutation, ALK positive and WT).

Objective Response Rate (ORR) will be graphically displayed for overall and also for each subgroup analysis using the Kaplan-Meier technique.

7.5.2.5 Duration of Response (DOR)

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 evaluable tumor assessment. The Subjects who started any subsequent anti-cancer therapy (excluding on-treatment palliative radiotherapy of non-target bone lesions, skin lesions or CNS lesions) without a prior reported progression will be censored at the last evaluable tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy. The 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.

Duration of Stable Disease will also be evaluated for subjects with SD as best response. Duration of SD is defined as the time between the date of first dose to the date of the first documented tumor progression (per RECIST 1.1) as assessed by the investigator, or death due to any cause, whichever occurs first. Censoring rules will be the same as for DOR analysis.

The above methods for DOR and duration of SD will be evaluated for pooled analysis and also in the following subgroups:

- Tumor Histology (Squamous and non-squamous)
- Tumor PD-L1 expression level (PD-L1 positive and PD-L1 negative protein expression)
- Infection Status (Non-HBV infected and HBV infected)
- Molecular Type (EGFR mutation, ALK positive and WT).

The DOR will be graphically displayed for overall and also for each subgroup analysis using the Kaplan-Meier technique.

A by-subject listing will be provided for OS, TTF, PFS, ORR and DOR.

7.6 Safety

All the safety analysis will be performed for all treated participants by HBV status and pooled. Analysis windows/analysis visits are outlined in Appendix 2.

7.6.1 Deaths

See Core Safety SAP.

7.6.2 Serious Adverse Events

See Core Safety SAP.

7.6.3 Adverse Events Leading to Discontinuation of Study Therapy

See Core Safety SAP.

7.6.4 Adverse Events Leading to Dose Modification

See Core Safety SAP.

7.6.5 Adverse Events

See Core Safety SAP.

7.6.6 Select Adverse Events

See Core Safety SAP.

7.6.7 Multiple Events

See Core Safety SAP.

7.6.8 Other Events of Special Interest

See Core Safety SAP.

7.6.9 Immune Mediated Adverse Events

See Core Safety SAP.

7.6.10 Clinical Laboratory Evaluations

Laboratory evaluations will be reported using both the US conventional unit and Standard International (SI) unit.

The analysis population for each laboratory test is restricted to treated participants who underwent that laboratory test. Laboratory tests (in addition to the tests specified below) with CTC criteria collected in the specific studies may also be included in the summaries. In addition, baseline laboratory results will be summarized using descriptive statistics for all treated participants.

7.6.10.1 Hematology

See Core Safety SAP.

7.6.10.2 Serum Chemistry

See Core Safety SAP.

7.6.10.3 Electrolytes

See Core Safety SAP.

7.6.10.4 Abnormal Thyroid Function Test

See Core Safety SAP.

7.6.10.5 Abnormal Hepatic Function Test

See Core Safety SAP.

7.6.11 Vital Signs and Pulse Oximetry

See Core Safety SAP.

7.6.12 Electrocardiogram

Descriptive summary will be provided for electrocardiogram parameters include (Heart Rate (bpm), PR Interval (msec), QRS width (msec), QT Interval (msec), QTc Bazett's (msec) and QTc

Fridericia's (msec)) by visit for all treated participants for observed values and changes from baseline for all treated participants by HBV status and pooled.

The overall ECG interpretation will be summarized by presenting the number and percentage of subjects with “Normal” and “Abnormal” by scheduled time-point. In addition, shift table will be provided to see the significant changes in ECG parameters. Also, abnormal findings will be listed separately.

By subject listing will be provided.

7.6.13 ECOG Performance Status

Summaries of ECOG performance will be provided for all treated participants by HBV status and pooled. In addition, continuous variable summary will be provided using descriptive statistics. A shift table will be provided to see the significant changes from baseline to post-baseline visits.

A by-subject listing of ECOG will be provided.

Classification of ECOG performance status is provided in Table 7.6-13.

Table 7.6-13: ECOG PERFORMANCE STATUS

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 self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

7.6.14 Pregnancy Testing

By-subject listing of pregnancy tests results will be provided for all treated female subjects.

7.7 Pharmacokinetics

Not applicable

7.8 Other Analyses

7.8.1 Biomarkers

The biomarker analysis will be performed for the Biomarker Subjects Population, which is defined as all treated participants with available biomarker data. Analyses for PD-L1 are described below.

Distribution of PD-L1 Expression

The following statistics of PD-L1 expression will be produced for pooled analysis and by tumor histology and molecular genotype:

- Listing of all PD-L1 immunohistochemistry (IHC) data
- Summary of tumor specimen acquisition and characteristics, all treated participants by HBV status and pooled.
- Summary statistics of PD-L1 expression with quantifiable PD-L1 expression
- 2 by 2 contingency table of PD-L1 status by response status (yes CR or PR; No SD or PD or unknown).

7.8.2 Outcomes Research Analyses

LCSS (Lung Cancer Symptom Scale)

The LCSS completion rates, defined as the proportion of questionnaires actually received out of the expected number will be calculated and summarized at each assessment point for all treated participants by HBV status and pooled. The baseline and change from baseline of the 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 will be done for all treated participants by HBV status and pooled. In addition, subgroup analysis will be performed 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).

By subject listing will be provided for all treated participants.

EuroQoL EQ-5D

The 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 for all treated participants by HBV status and pooled. 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. Subject's overall health state on a visual analog scale (EQ-VAS) at each assessment time point will be summarized using descriptive statistics (N, mean, SD, median, 25th and 75th percentiles).

The N3 model based on ordinary least square regression at the aggregate level was used to generate a Chinese general population-based three level EuroQol five-dimensions (EQ-5D-3L) social value set[6]. Value set for Chinese population will be used to get utility values for each individual. The baseline and change from baseline of the EQ-5D scores at each assessment point will be summarized using descriptive statistics.

The preference scores are calculated from the following algorithm,

Score 1 - Constant - MOx - SCx - UAx - PDx - ADx - N3

MO, SC, UA, PD and AD are the five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). x is the three levels for each dimension (1 no problems, 2 some/ moderate problems, and 3 extreme problems).
Coefficient generated from N3 model is provided in below table

	Value for each dimension (x)	Coefficient
Constant		0.039
MO	1	0
	2	0.099
	3	0.246
SC	1	0
	2	0.105
	3	0.208
UA	1	0
	2	0.074
	3	0.193
PD	1	0
	2	0.092
	3	0.236
AD	1	0
	2	0.086
	3	0.205
N3		0.022

All summaries for EQ-5D will be done for all treated participants for pooled analysis 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).

By subject listing will be provided for all treated participants.

[redacted]

8 CONVENTIONS

The following conventions may be used for imputing partial dates for analyses requiring dates:

For death dates, the following conventions will be used for imputing partial dates:

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day. The imputed date will be compared to the last known date alive and the maximum will be considered as the death date.
- If the month or the year is missing, the death date will be imputed as the last known date alive
- If the date is completely missing but the reason for death is present the death date will be imputed as the last known date alive

For date of progression, the following conventions will be used for imputing partial dates:

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day.
- If the day and month are missing or a date is completely missing, it will be considered as missing.

  In cases where the date of death is present and complete, the imputed progression date will be compared to the date of death. The minimum of the imputed progression date and date of death will be considered as the date of progression.

For missing and partial adverse event onset dates, imputation will be performed using the Adverse Event Domain Requirements Specification[3].

For missing and partial adverse event resolution dates, imputation will be performed as follows (these conventions may change):

- If only the day of the month is missing, the last day of the month will be used to replace the missing day
- If the day and month are missing or a date is completely missing, it will be considered as missing.

Missing and partial non-study medication domain dates will be imputed using the derivation algorithm described in 4.3.3 of BMS Non-Study Medication Domain Requirements Specification[4].

For other partial/missing dates, the following conventions may be used:

- If only the day of the month is missing, the 15th of the month will be used to replace the missing day.
- If both the day and the month are missing, “July 1” will be used to replace the missing information.
- If a date is completely missing, it will be considered as missing.

The following conversion factors will be used to convert days to months or years: 1 month 30.4375 days and 1 year 365.25 days.

Duration (e.g. time from first diagnosis to first dosing date, duration of response, and time to response) will be calculated as follows:

Duration (Last date - first date + 1)

For the LCSS symptom burden index, values will be imputed for missing symptom-specific items by using values equal to the average of the nonmissing symptom-specific items if at least half the items are completed. If less than half of the symptom-specific items are completed data will be treated as missing. For the LCSS three item global index, missing data will not be imputed to minimize bias. If the score for one item is missing, the index score will be treated as missing.

For the EQ-5D, no adjustment will be made for missing data when scoring the EQ-5D index or the EQ-5D VAS.

All statistical analyses will be carried out using SAS (Statistical Analysis System software, SAS Institute, North Carolina, USA) unless otherwise noted.

9 CONTENT OF REPORTS

All analyses described in this SAP will be included in the Clinical Study Report except where otherwise noted. Refer to the Data Presentation Plan for mock-ups of all tables and listings.

10 REFERENCES

1. Core Safety Statistical Analysis Plan for Multiple Indications, Nivolumab Program, Protocols C A209, V 5.0.
2. Global Biometric Sciences, Core Safety Data Presentation Plan, BMS 936558, Nivolumab, CSR, Reports, V 6.1.
3. Adverse Event Domain Requirements Specification Bristol Myers Squibb Co. PRI. Version 2.1.2 April 23, 2012.
4. Non-Study Medication Domain Requirements Specification Bristol Myers Squibb Co. PRI. Version 2.2 April 24, 2012.
5. Waterhouse DM, Horn L, Reynolds CH, et al. Safety profile of nivolumab administered as 30-minute (min) infusion: Analysis of data from CheckMate 153. 2016 ASCO Annual Meeting. J Clin Oncol 34, 2016 (suppl; abstr 3059).
6. Gordon G. Liu, Hongyan Wu, et al. Chinese Time Trade-Off Values for EQ-5D Health States. Value Health 2014; 17: 597-604.

APPENDIX 1 SCHEDULE OF ACTIVITIES

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.

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, and other biomarkers. 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

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)

Procedure	Cycle 1 Day 1 (Q2 weeks)	Subsequent cycles (Q2 weeks)	Notes
			Note: Cycle 1 Day 1 laboratory assessments do not need to be repeated if performed within 14 days prior to 1st dose.
[redacted]			
Additional research collection	X	X	See Section 9.8.1
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)

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

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

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.

APPENDIX 2 DEFINITION OF ANALYSIS VISIT

Observation/event based visit schedule

- Determine the starting date-time (lower bound) for each planned visit
- Compare observation/event date-time to visit intervals, to slot each observation/event into a planned visit
- If observation/event date-time is less than lower bound of first visit then AVISIT and AVISITN are equal to the first visit identifiers and if greater than the lower bound of the last visit then AVISIT and AVISITN are equal to the last visit identifiers
- Compare observation/event date-time with visit boundaries and set AVISIT equal to the planned visitn where the observation/event date-time is between lower bound of visitn and visitn+1.
- If observation/event date-time is equal to the lower bound of visit , slot into current (visitn) or previous (visitn-1) based on the protocol schedule.
- If time is not collected or missing for either the observation or the lower boundary, a date-date comparison is performed. If the dates are equal then the observation/event is slotted into the current or previous study period based on the Protocol Slotting Schedule.
- If observation date is missing, then AVISIT will be set to the visit identifiers associated with the collection instrument visit code for that domain.

If the visit code from the collection instrument is an unscheduled visit, the visit identifiers associated with the scheduled visit immediately preceding the unscheduled visit will be used