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Clinical Protocol CA209171

An Open-Label, Multicenter Clinical Trial with Nivolumab (BMS-936558) Monotherapy in Subjects with Advanced or Metastatic Squamous Cell (Sq) Non-Small Cell Lung Cancer (NSCLC) who Have Received at Least One Prior Systemic Regimen for the Treatment of Stage IIIb/IV SqNSCLC

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Revised Protocol 05

Medical Monitor

Angelic A. Ranck, MD

[redacted]

Replaces all version(s) of this protocol with this revised protocol, and please provide a copy of this revised protocol to all study personnel under your supervision and archive the previous versions.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 05	10-Sep-2018	• OS will be collected for at least 3 years and up to 5 years from the first dose of study therapy. • Dose delay, criteria to resume treatment, and discontinuation updated to align with program standards for safety • Study personnel updated
Revised Protocol 04	26-Oct-2016	Incorporates Amendment 04 + Administrative Letters 02 & 03
Amendment 04	26-Oct-2016	Keys changes: - Adjustment to PS 0-1 and PS 2 subgroup sample numbers - Changes to informed consent procedure for treatment beyond disease progression - Clarification of SAE reporting to to within 100 days of discontinuation of drug - [redacted] - Addition that dose must be recalculated if weight on the day of dosing differs by > 10% from the weight used to calculate the dose
Administrative Letter 03	20-May-2016	Clarification of SAE reporting to within 100 days of discontinuation of drug
Administrative Letter 02	14-Aug-2015	The study design and schematics changed to adjust PS 0-1 and PS 2 subgroup sample numbers Clarification of pregnancy testing to serum or urine.
Revised Protocol 03	18-Jun-2015	Incorporates Amendment 03
Amendment 03	18-Jun-2015	Three key changes were made to this protocol: the sample size was reduced from 1800 to 950 (with 15% screening failure rate, 800 will be treated); second-line lung cancer patients will now be allowed to enroll in the study; and the randomization at one year into Cohort A and Cohort B has been removed.
Revised Protocol 02	26-Feb-2015	• Study Director and Medical Monitor were changed • The use of a condom with spermicide was demoted from a highly effective to less effective method of contraception [redacted] • Table 5.1-3 Pregnancy test had additional language added for clarification [redacted]
Revised Protocol 01	21-Nov-2014	Incorporates Administrative Letter 01 and Amendment 01.
Amendment 01	21-Nov-2014	• The inclusion criteria have been expanded and the exclusion criteria have been minimized in order to expand the subject population.

Document	Date of Issue	Summary of Change
		• The background section has also been updated to reflect the most recently available data. • The options for palliative local therapy have also been expanded to meet the needs of the current patient populations. • Randomization after 1 year to subjects who are still benefitting from treatment and achieved a partial or complete response to offer insight into the optimal treatment duration of nivolumab has been added. After 1 year of therapy, subjects will be randomized to continue nivolumab monotherapy (Cohort A) or discontinue therapy with the option of retreatment disease progression (Cohort B). • The requirement to have a separate assessment plan for the subjects in the Performance Status 2 (PS2) subgroup has been eliminated. [redacted] • Initial tumor assessments have also been changed to occur at Week 8 instead of Week 6. • The statistical section has been reformatted. • The phrase "rate and frequency" has been changed to the term "incidence" throughout the protocol. • The term "Adverse Events of Special Interest" has been changed to "Select Adverse Events." • The Performance Status groups were renamed "Subgroup" (from "Cohort") to avoid confusion with the randomized cohorts. • Treatment discontinuation criteria were moved from Section 3.5 to the newly created Section 4.6.5.1 to follow the nivolumab protocol structure. • The requirement for electrocardiograms has been removed as these tests are not done within the nivolumab clinical development program any more.
Administrative Letter 01	12-May-2014	The title of this protocol has been modified for consistency with the BMS conventions for protocols in the nivolumab program.
Original Protocol	18-Apr-2014	Not applicable

SYNOPSIS

Clinical Protocol CA209171

Protocol Title: An Open-Label, Multicenter Clinical Trial with Nivolumab (BMS-936558) Monotherapy in Subjects with Advanced or Metastatic Squamous Cell (Sq) Non-Small Cell Lung Cancer (NSCLC) who Have Received at Least One Prior Systemic Regimen for the Treatment of Stage IIIb/IV SqNSCLC

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Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Nivolumab solution for injection, 3 mg/kg, intravenous (IV) infusion over 60 minutes every 2 weeks, until disease progression, unacceptable toxicity, withdrawal of informed consent, or end of study.

Study Phase: II

Research Hypothesis: High-grade (CTCAE v4.0 Grade 3 or higher) treatment-related, select adverse events occur with a low frequency in subjects with advanced or metastatic squamous non-small cell lung cancer (SqNSCLC) treated with nivolumab monotherapy.

Objectives:

Primary Objective:

- To determine the incidence of high-grade (CTCAE v4.0 Grades 3-4), treatment-related, select adverse events in subjects with advanced or metastatic SqNSCLC who progressed during or after at least 1 systemic therapy.

Secondary Objectives:

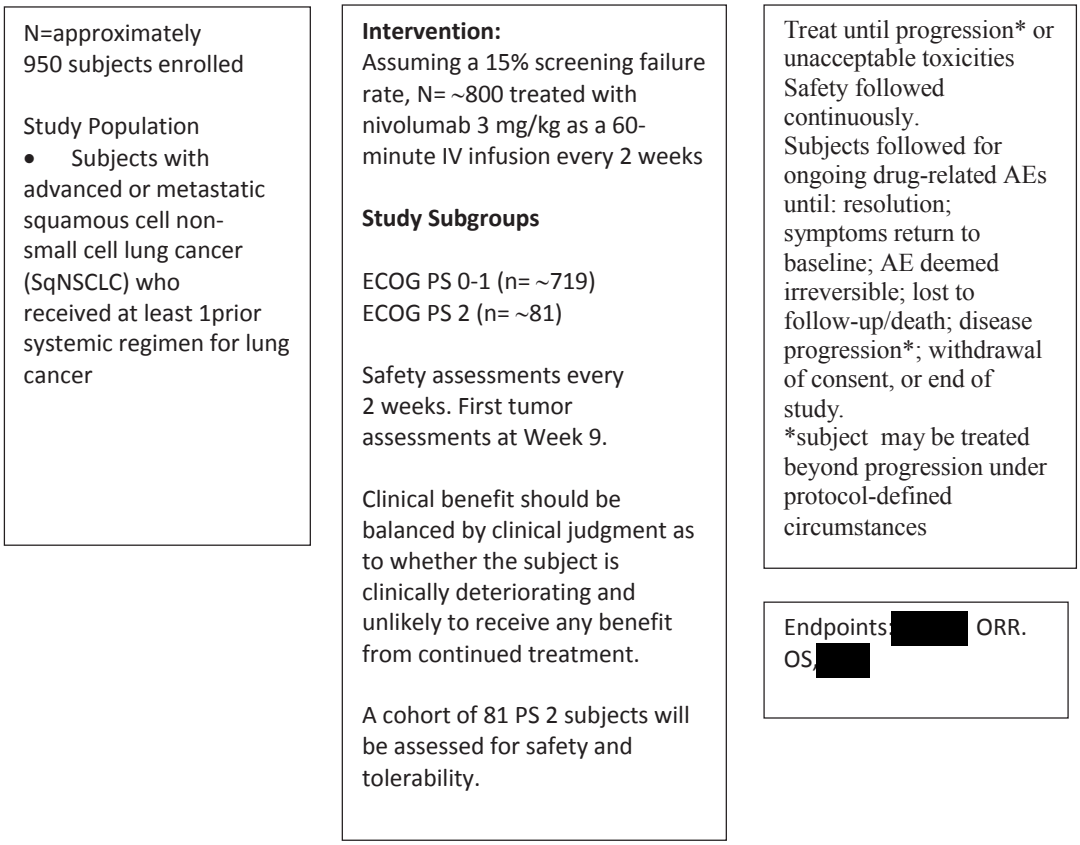
- To determine the incidence and to characterize the outcome of all high-grade (CTCAE v4.0 Grades 3-4), select adverse events in subjects with advanced or metastatic SqNSCLC who have progressed during or after at least 1 prior systemic therapy
- To estimate overall survival (OS) in all treated subjects
- To estimate investigator-assessed objective response rate (ORR)

[redacted]

Study Design: The study will include subjects with histologically- or cytologically-documented SqNSCLC who have progressed during or after a minimum of 1 prior platinum doublet-based chemotherapy regimen for advanced or metastatic disease. Subjects will be treated with 3 mg/kg of nivolumab IV every 2 weeks until disease progression, unacceptable toxicity, withdrawal of consent, or end of study. Subjects will undergo screening evaluations to determine eligibility within 28 days prior to first dose following signed informed consent. Each 14-day dosing period will constitute a cycle.

The Scientific Steering Committee will provide guidance and scientific expertise on the clinical risk/benefit ratio closely following a defined Safety Management Plan.

Study Schematic:



Study Population:

Key Inclusion Criteria

a) Eastern Cooperative Oncology Group (ECOG) Performance Status (PS):

   i) PS 0 to 1 (Subgroup1)

   ii) PS 2 (Subgroup 2; minimum of 81 treated subjects. The Scientific Steering Committee will provide guidance and scientific expertise on the risk/benefit ratio following a Safety Management Plan).

b) Subjects with histologically or cytologically-documented SqNSCLC who presented with stage IIIb/stage IV disease or who developed recurrent or progressive disease following prior definitive therapy for localized or local advanced disease. A fresh biopsy is not required to take part in the study.

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

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

   ii) Subjects 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.

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

d) Subjects with CNS metastases:

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

OR

ii) Subjects are eligible if they have previously untreated CNS metastases that are neurologically asymptomatic. In addition, subjects must be either off corticosteroids or on a stable or decreasing dose of ≤10 mg daily prednisone (or equivalent)

Key exclusion criteria:

a) Subjects with untreated, symptomatic CNS metastases are excluded

b) Subjects with carcinomatous meningitis are excluded.

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

Study Drug for CA209-171		
Medication	**Potency**	**IP/Non-IP**
Nivolumab Injection BMS-936558-01	10 mg/mL; 100 mg/Vial; 10 or 5 vials per carton Open-label	IP

Study Assessments: 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 subject's medical record and should not be provided to BMS unless specifically requested.

The following assessments should be monitored starting on Cycle 1 Day 1 and will continue as per the schedule in the Time and Events Tables at the specified frequency:

- AEs continuously throughout the study
- Physical examination and physical measurements including weight, and ECOG PS
- [redacted]
- [redacted]
- [redacted]

Mandatory tumor assessments are to be completed at Weeks 9 and 52 (±5 days). Additional tumor assessments should be performed as required by local standards of care or at the investigator's discretion as discussed in the Time and Events Schedule and are recommended every 8-12 weeks until disease progression per RECIST 1.1 criteria (or discontinuation of study treatment in subjects receiving nivolumab beyond progression), subject lost to follow up, withdrawal of study consent by subject, or end of study. Overall survival will be collected for at least 3 years and up to 5 years from the first dose of study therapy, as indicated in the assessment tables.

Statistical Considerations:

Sample Size: A total of 950 subjects who are evaluated based on the ECOG PS will be enrolled; Subgroup 1 will enroll subjects with PS 0-1 (n ~ 855), and Subgroup 2 will enroll subjects with PS 2 (n ~ 95). The screen failure rate is anticipated to be 15%, which results to approximately 719 and 81 treated subjects in Subgroup 1 and Subgroup 2, respectively.

With n=800 subjects, about 4 subjects will experience a rare adverse event with 0.5% true cumulative event rate with a rate estimate within a 95% confidence interval (CI) (0.1%-1.3%). Approximately 2 subjects with events and a 95% CI of (0.1%-0.9%) for assumed true event rate of 0.25% are projected.

The 95% CI is calculated using the Clopper-Pearson method in PASS12.

Endpoints: The primary endpoint is the incidence of high-grade (CTCAE v4.0 Grades 3-4), treatment-related, select adverse events

The secondary endpoints include:

- Incidence of high grade (Grades 3-4) select adverse events
- Median time to onset and median time to resolution (Grades 3-4) of select adverse events
- OS
- ORR

[redacted]

Analyses: The analysis of primary, secondary (excluding objective response rate), and exploratory endpoints will be reported for the full safety analysis set and subgroups based on ECOG PS. ORR will be reported for the response evaluable analysis set and by PS subgroups and randomized cohorts

Analysis of Primary Endpoints

The number and percentage of subjects who report high-grade (Grades 3-4), treatment-related, select adverse events will be summarized for all treated subjects and by subgroups. Treatment-related, select adverse events will be tabulated using worst grade per NCI CTCAE V4.0 criteria by system organ class (SOC) and Medical Dictionary for Regulatory Affairs (MedDRA) preferred terms.

Analysis of Secondary Endpoints

Incidence of high grade (Grades 3-4) select adverse events, regardless of relationship to study treatment will be analyzed in the same manner as the primary endpoint.

Descriptive statistics including time to onset and time to resolution of select adverse events and OS will be estimated using Kaplan-Meier (KM) product limit method for all treated subjects by subgroups and randomized cohorts. Median time to onset, median time to resolution, and median overall survival, if estimable, will be presented together with their 95% confidence interval (CI) using Brookmeyer and Crowley method. If medians are not estimable, estimation of other percentiles (eg, 10th or 25th quartile) may be considered.

OS rates at Years 1 and 2, together with their 95% CIs, will also be estimated using KM estimates on the OS curves. Associated 2-sided 95% CIs will be calculated using the Greenwood formula.

The ORR will be summarized by binomial response rates and their corresponding two-sided 95% exact CIs using the Clopper-Pearson method. This analysis will be performed for all response evaluable subjects. This analysis will also be performed by subject subgroups.

[redacted]

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[redacted]

1.3 Objectives(s)

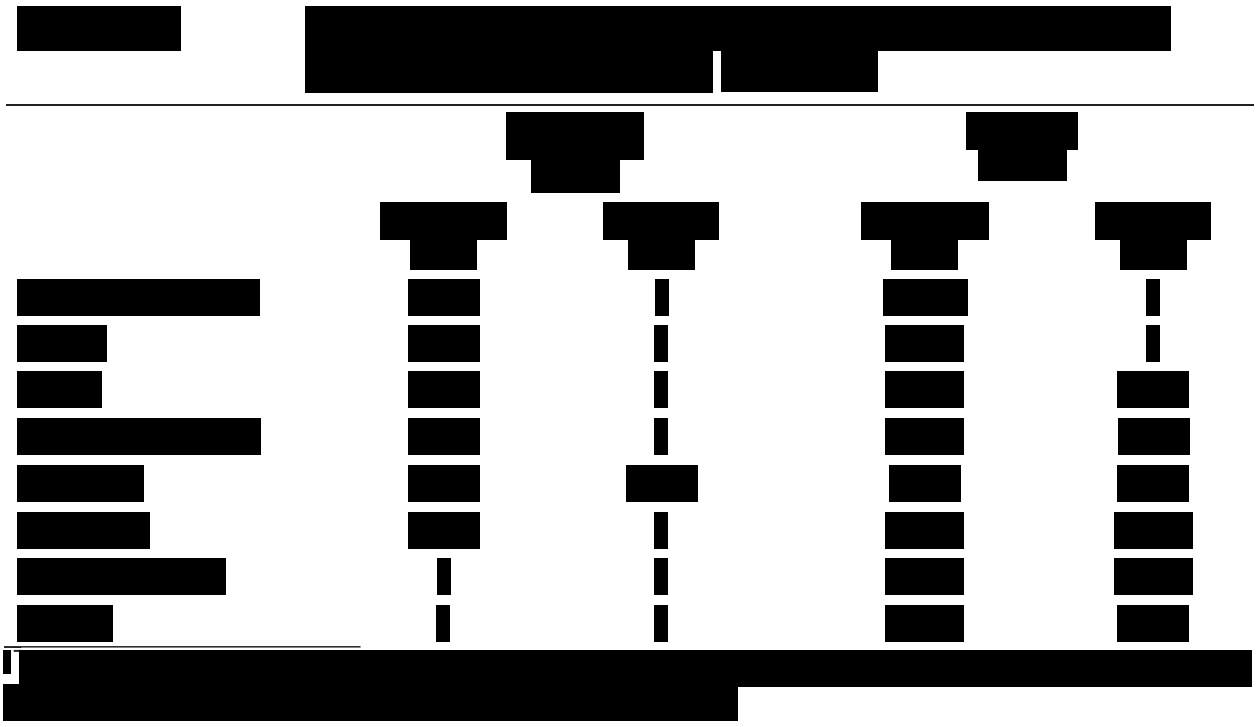
1.3.1 Primary Objective

- To determine the incidence of high-grade (CTCAE v4.0 Grades 3-4), treatment-related, select adverse events in subjects with advanced or metastatic SqNSCLC who progressed during or after at least 1 systemic therapy.

1.3.2 Secondary Objectives

- To determine the incidence and to characterize the outcome of all high-grade (CTCAE v4.0 Grades 3-4), select adverse events in subjects with advanced or metastatic SqNSCLC who have progressed during or after at least 1 prior systemic therapy
- To estimate overall survival in all treated subjects
- To estimate investigator-assessed ORR

[redacted]



[redacted]

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

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

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

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

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

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

2.2 Institutional Review Board/Independent Ethics Committee

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

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

2.3 Informed Consent

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

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

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

Investigators must:

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

4) 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.
5) If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

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

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

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

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

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

The study will include subjects with histologically- or cytologically-documented SqNSCLC who have progressed during or after a minimum of 1 prior systemic treatment for advanced or metastatic disease. Subjects will be treated with 3 mg/kg of nivolumab IV every 2 weeks until disease progression, unacceptable toxicity, withdrawal of consent, or end of study. Subjects will undergo screening evaluations to determine eligibility within 28 days prior to first dose following signed informed consent (as described in Table 5.1-1). Each 14-day dosing period will constitute a cycle. Please refer to Table 5.1-2 for additional procedures to be performed during study treatment.

The Scientific Steering Committee (Section 7) will provide guidance and scientific expertise on the clinical risk/benefit ratio closely following a defined Safety Management Plan.

Subjects will be evaluated in 2 separate subgroups: ECOG PS 0-1 subjects and PS 2 subjects (Table 3.1-1).

Enrollment of new subjects on the study will continue until the target recruitment is met. At the conclusion of the study, subjects 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. After marketing authorization, if permitted by the local country, subjects within the study may access locally available drug.

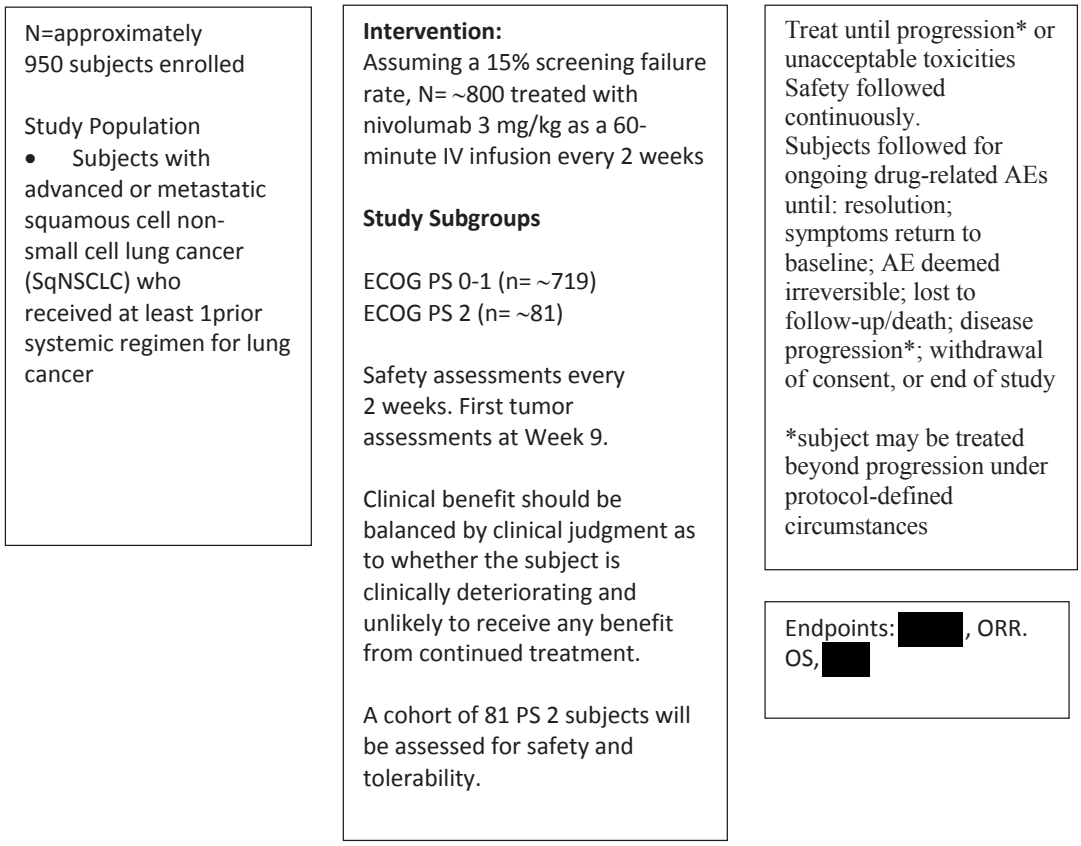
In this study, overall survival is a key endpoint. Post study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study drug must continue to be followed for collection of outcome and/or survival follow-up data as required and until death or the conclusion of the study. The study will close after the last enrolled subject completes at least 3 years of follow-up

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

Table 3.1-1: Subject Subgroup

(Subgroup Number) Total study population n=950	**Disease Criteria**
Subgroup 1: ECOG PS 01- (N approximately 855)	• ECOG Performance Status 0 to 1 • Failed 1 or more prior systemic therapy • Balance enrolling second-line and third-line subjects
Subgroup 2: PS2 (N approximately 95)	• ECOG Performance Status 2 • Failed 1 or more prior systemic therapy • Balance enrolling second-line and third-line subjects

Figure 3.1-1: Study Design Schematic



3.2 Post Study Drug Access to 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.

3.3 Study Population

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

3.3.1 Inclusion Criteria

1) Signed Written Informed Consent

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

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

2. Target Population

a) ECOG PS:

   i) PS 0 to 1 (Subgroup 1)

   ii) PS 2 (Subgroup 2; minimum of 95 enrolled (81 treated) subjects. The Scientific Steering Committee will provide guidance and scientific expertise on the risk/benefit ratio following a Safety Management Plan).

b) Subjects with histologically or cytologically-documented SqNSCLC who presented with stage IIIb/stage IV disease or who developed recurrent or progressive disease following prior definitive therapy for localized or local advanced disease. NOTE: A fresh biopsy is not required to take part in the study.

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

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

   ii) Subjects 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.

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

d) Subjects must have evaluable 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.

e) Subjects with CNS metastases:

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

   OR

   ii) Subjects are eligible if they have previously untreated CNS metastases that are neurologically asymptomatic. In addition, subjects must be either off corticosteroids or on a stable or decreasing dose of ≤10 mg daily prednisone (or equivalent).

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

g) Prior palliative radiotherapy must have been completed at least 14 days prior to study drug administration. See Section 3.4.3.1 for guidance on palliative radiotherapy during study treatment.

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

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

j) Screening laboratory values must meet the following criteria prior to commencement of treatment:

i) WBCs ≥ 2000/μL

ii) Neutrophils ≥ 1500/μL

iii) Platelets ≥ 100 X10^3/μL

iv) Hemoglobin ≥ 9.0 g/dL

v) Serum creatinine of ≤ 1.5 X ULN or creatinine clearance (CrCl) > 40 mL/minute (using Cockcroft/Gault formula)

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

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

vi) AST ≤ 3 X ULN

vii) ALT ≤ 3 X ULN

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

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

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

m) Prior lines of antineoplastic therapy, including chemotherapy, hormonal therapy, immunotherapy, surgical resection of lesions, non-palliative radiation therapy, or standard or investigational agents for treatment of NSCLC, must be completed 28 days prior to the first dose of nivolumab

3. Age and Reproductive Status

a) Males and Females, ages 18 or older

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

c) Women must not be breastfeeding

d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with nivolumab plus approximately 5 half-lives of nivolumab plus 30 days (duration of ovulatory cycle) for a total of 5 months post-treatment completion.

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with nivolumab plus approximately 5 half-lives of the study drug plus 90 days (duration of sperm turnover) for a total of 7 months post-treatment completion.

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

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.

At a minimum, WOCBP and male subjects who are sexually active with WOCBP must agree to the use of one of the highly effective methods of contraception.

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

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

1) Progestogen only hormonal contraception associated with inhibition of ovulation
2) Hormonal methods of contraception including oral contraceptive pills containing combined estrogen + progesterone, vaginal ring, injectables, implants, transdermal, and intrauterine hormone releasing systems (IUS).
3) Nonhormonal IUDs, such as ParaGard
4) Bilateral tubal occlusion
5) Vasectomized partner with documented azoospermia 90 days after procedure
    a) Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.
6) Intrauterine hormone-releasing system (IUS)
7) Complete abstinence
    a) Complete abstinence is defined as the complete avoidance of heterosexual intercourse
    b) Complete abstinence is an acceptable form of contraception for all study drugs and must be used throughout the duration of the study treatment (plus 5 half-lives of the investigational drug plus 30 days).
    c) It is not necessary to use any other method of contraception when complete abstinence is elected.
    d) Subjects who choose complete abstinence must continue to have pregnancy tests.
    e) Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.
    f) The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

UNACCEPTABLE METHODS OF CONTRACEPTION

1) Vaginal sponge with spermicides
2) Progestin-only pills

3) Cervical cap with spermicides
4) Diaphragm with spermicides
5) Periodic abstinence (calendar, symptothermal, post-ovulation methods)
6) Withdrawal (coitus interruptus)
7) Spermicide only
8) Lactation amenorrhea method (LAM)
9) Male condoms with or without spermicide for partners of female subjects, as the only method of contraception
10) Female condoms
11) A male and a female condom must not be used together

3.3.2 Exclusion Criteria

1) Target Disease Exceptions

a) Subjects with untreated, symptomatic CNS metastases are excluded.

b) Subjects with carcinomatous meningitis are excluded.

2) Medical History and Concurrent Diseases

a) Subjects with active, known or suspected autoimmune disease. Subjects with Type I diabetes mellitus, residual hypothyroidism due to an autoimmune condition requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

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

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

d) Other active malignancy requiring concurrent intervention

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

f) Any serious or uncontrolled medical disorder or active infection that, in the opinion of the investigator, may increase the risk associated with study participation, study drug administration, or would impair the ability of the subject to receive protocol therapy

g) 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.

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

i) Known alcohol or drug abuse

j) Subjects who received prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways) or who have previously taken part in a randomized BMS clinical trial for nivolumab or ipilimumab.

3) Physical and Laboratory Test Findings

a) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).

b) Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic infection.

4) Allergies and Adverse Drug Reactions

a) History of severe hypersensitivity reactions to other monoclonal antibodies

b) As of Amendment 01, this criterion is not applicable.

5) Sex and Reproductive Status

a) WOCBP who are pregnant or breastfeeding

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

6) As of Amendment 01, this section was removed.

a) As of Amendment 01, this criterion was removed.

b) As of Amendment 01, this criterion was removed.

c) As of Amendment 01, this criterion was removed.

d) As of Amendment 01, this criterion was removed.

e) As of Amendment 01, this criterion was removed.

7) Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated

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

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

3.3.3 Women of Childbearing Potential

A woman of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

Females treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The durations of the washout period below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels. If the serum FSH level is >40 mIU/mL at any time during the washout period, the woman can be considered postmenopausal:

1 week minimum for vaginal hormonal products (rings, creams, gels)

4 week minimum for transdermal products

8 week minimum for oral products

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

[redacted]

[redacted]

3.5 Discontinuation of Subjects Following Any Treatment with Study Drug

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

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

In the case of pregnancy, the investigator must immediately notify BMS Medical Monitor/designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate

manner. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

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

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

3.6 Post-Study Drug Study Follow up

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

The subjects will be followed up for select AEs for a minimum of 100 days from the last dose of study therapy and for ongoing drug-related AEs until resolved, return to baseline or deemed irreversible, or until lost to follow-up or withdrawal of study consent.

One of the endpoints is overall survival, and every attempt will be made to obtain survival status every 3 months or until death, lost to follow-up, withdrawal of study consent, or end of study.

3.6.1 Withdrawal of Consent

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

3.6.2 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up

is defined by the inability to reach the subject after a minimum of 3 documented phone calls, faxes, or emails as well as lack of response by subject to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

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

4 TREATMENTS

4.1 Study Treatments

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

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

[redacted]

4.2 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, the investigational product is nivolumab.

4.3 Non-investigational Product

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

In this protocol, non-investigational products are not applicable.

4.4 Storage and Dispensing

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

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

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

For non-investigational product, if marketed product is utilized, it should be stored in accordance with the package insert, summary of product characteristics (SmPC), or similar.

[redacted]

4.6.1 Management of Select Adverse Events

In some cases, the natural history of AEs associated with immunotherapy can differ from and be more severe than AEs caused by agents belonging to other therapeutic classes. Early recognition and management may mitigate severe toxicity. Evaluation and management guidelines for the following groups of AEs were developed to assist investigators and can be found in the Investigator Brochure:

- Pulmonary toxicity
- Gastrointestinal toxicity (diarrhea or colitis)
- Endocrinopathies
- Hepatotoxicity (including asymptomatic LFT elevations)
- Renal toxicity
- Skin toxicity
- Neurological toxicity

For subjects expected to require more than 4 weeks of corticosteriods or other immunosuppressants to manage the AE, consider the recommendations provided in the Investigator Brochure. Tumor assessments for all subjects should continue as per local standard of care and guidelines, even if dosing is interrupted.

4.6.2 Nivolumab Dose Delay Criteria

Nivolumab administration should be delayed for the following:

- Grade2 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
- Grade ≥3 AST, ALT, total bilirubin will require dose discontinuation
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication

4.6.3 Nivolumab Dose Reductions and Escalations

Nivolumab dose reductions and escalations are not permitted.

4.6.4 Criteria to Resume Treatment with Nivolumab

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

- Subjects may resume treatment in the presence of Grade 2 fatigue
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- Subjects with Grade 2 AST, ALT and/or Total Bilirubin Abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for re-initiation of treatment if discussed with and approved by the 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 (or designee). Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

4.6.5 Treatment Discontinuation Criteria

Tumor assessments for <u>all</u> subjects should continue as per protocol even if dosing is discontinued.

4.6.5.1 Nivolumab Dose Discontinuation

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-initiation period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reactions, infusion reactions, and endocrinopathies::
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reaction, infusion reactions, and endocrinopathies
  - Grade 3 drug-related endocrinopathies, adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Grade ≥ 3 drug-related AST, ALT or Total Bilirubin requires discontinuation*
    - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2x ULN

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

- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 drug-related endocrinopathy adverse events, such as, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor.
- Any dosing interruption lasting > 6 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the BMS Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted
  - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor (or designee).

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

4.6.6 Treatment Beyond Disease Progression

As described in Section 1.1.4, accumulating evidence indicated a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease.[49]

Subjects treated with nivolumab will be permitted to continue treatment beyond initial Investigator-assessed RECIST 1.1-defined progressive disease as long as they meet the following criteria:

- Investigator-assessed clinical benefit and do not have 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)
- Subject provides written informed consent prior to receiving additional nivolumab treatment using an ICF describing any reasonably foreseeable risk or discomforts or other alternative treatment options

The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinical deteriorating and unlikely to receive any benefit from continued treatment with nivolumab.

All decisions to continue treatment beyond initial progression must be discussed with the BMS Medical Monitor and documented in the study records.

Subjects must sign a separate informed consent form to receive treatment beyond progression.

Subjects should discontinue study therapy upon evidence of further progression, defined as an additional ≥10% increase in tumor burden volume from time of initial progression (including all target lesions and new measurable lesions).

Global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at the time should be reported as symptomatic deterioration. Every effort should be made to document objective progression (ie, radiographic confirmation) even after discontinuation of treatment.

4.6.7 Treatment of Nivolumab-Related Infusion Reactions

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

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

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

Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional nivolumab administrations.

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

Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or

bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further nivolumab will be administered at that visit. Administer diphenhydramine 50 mg IV and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); these should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV 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 subject as follows: recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the Investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued.

Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms. In case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

4.7 Blinding/Unblinding

Not applicable

4.8 Treatment Compliance

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

4.9 Destruction of Study Drug

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

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

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

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

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

4.10 Return of Study Drug

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

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

Arrangements for the return of study drug will be made by the responsible Study Monitor.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Procedure Outline (CA209171)

Procedure	Screening Visit[a]	Notes
Eligibility Assessments		
Informed Consent	X	
Inclusion/Exclusion Criteria	X	Assessed prior to first dose
Medical History	X	Medical history will include smoking history, comorbidities, particularly chronic pulmonary and chronic cardiovascular diseases following international established categories (eg, NYHA for cardiac insufficiency). Mutation status of EGFR and ALK will be collected and ROS, MET, KRAS, and BRAF will be collected, if available. Additional biopsies for mutation status, if not previously tested, are not required.
Safety Assessments		
HIV testing (in Germany only)	X	
Physical Examination	X	Includes height, weight, and ECOG PS. Focused physical exam may be performed at screening if clinically indicated.
ECOG Performance Status	X	Subgroup 1: PS 0-1 Subgroup 2: PS 2
Vital Signs and Oxygen Saturation	X	Temperature, BP, HR, RR, O2 saturation by pulse oximetry at rest (also monitor amount of supplement oxygen if applicable). Obtain vital signs at screening visit and within 72 hours of first dose.
Assessment of Signs and Symptoms	X	After obtaining Informed Consent, assess all signs and symptoms within 14 days of first dose, prior to study treatment initiation.
[redacted]	[redacted]	[redacted]
Serious Adverse Events Assessment	X	
Adverse Events Assessment	X	

Table 5.1-1: Screening Procedure Outline (CA209171)

Procedure	Screening Visit[a]	Notes
[redacted]	[redacted]	[redacted]
Pregnancy Test	X	Performed within 24 hours prior to first dose for WOCBP only (serum or urine as required by the standard of care at the site)
Additional Assessments		
[redacted]	[redacted]	[redacted]
Efficacy Assessment		
Screening/Baseline Tumor Assessment		Chest, abdomen, pelvis, brain, and all other known sites of disease within 28 days prior to first dose of study therapy. Subjects must have evaluable 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.

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; BP = blood pressure; BUN = blood urea nitrogen; CBC = complete blood count; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C antibody; HR = heart rate; LDH = lactate dehydrogenase; O2 = oxygen; PS = Performance Status; RR = respiratory rate; TFT = Thyroid Function Test ; TSH, thyroid stimulating hormone; WOCBP = women of child bearing potential.

[a] Within 28 days before start of nivolumab

Table 5.1-2: CA209171 On-treatment Assessments

Procedure	Each Cycle (every 2 weeks)	Every 2 Cycles (every 4 weeks)	Every 3 Cycles (every 6 weeks)	Week 9	Week 52	Notes
Safety Assessments						
Physical Measurements (including Performance Status)	X					Collect weight and ECOG Performance Status within 72 hours prior to dosing. Focused physical examination may be performed if clinically indicated.
Vital Signs and Oxygen Saturation	X					Within 72 hours prior to dosing, tests includes temperature, BP, HR, RR, O2 saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable) prior to dosing and at any time a subject has any new or worsening respiratory symptoms.
Serious Adverse Event Assessment	X					Assessed using NCI CTCAE v 4.0
Adverse Events Assessment	X					Assessed using NCI CTCAE v 4.0
[redacted]	[redacted]					
[redacted]	[redacted]		[redacted]			[redacted]
Pregnancy Test		X				Completed more frequently if required by local standards (serum or urine as required by standard of care at the site).

Table 5.1-2: CA209171 On-treatment Assessments

Procedure	Each Cycle (every 2 weeks)	Every 2 Cycles (every 4 weeks)	Every 3 Cycles (every 6 weeks)	Week 9	Week 52	Notes
Assessments						
Tumor Scans				X	X	Mandatory tumor assessments are to be done at Weeks 9 and 52 (±5 days) according to RECIST 1.1 criteria. Additional assessments should be performed according to local standards of care or at the investigator's discretion and are recommended every 8-12 weeks. Assessments should include chest, abdomen, and all known or suspected sites of disease.
[redacted]						[redacted]
Survival	X					
Clinical Drug Supplies						
Administration of Study Drug	X					All subjects continue treatment every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of informed consent. Treatment for all subjects can continue beyond initial investigator-assessed progression, if the subject has investigator-assessed clinical benefit and is tolerating the study drug. Record Study Drug Infusion start and stop times.

BP = blood pressure; CBC = complete blood count; HR = heart rate; [redacted] NCI CTCAE = National Cancer Institute Common Terminology Criteria for AEs; O2 = oxygen; PS = Performance Status; RR = respiratory rate.

[a] CBCs with differential includes white blood cell count, lymphocyte count, absolute neutrophil count, hemoglobin, hematocrit, and platelet count. Results to be obtained prior to dosing on infusion days.

[redacted]

Table 5.1-3: CA209171 Off-Treatment Follow Up Assessments				
Procedure	**FU1 6 weeks (±2 weeks) after last dose**	**FU2 16 weeks (±2 weeks) after last dose**	**Further Follow-Up Every 3 months (±1 month) after FU2**	**Notes**
Safety Assessments				
Physical Examinations	X	X		Collect weight and ECOG Performance Status. Focused physical examination may be performed if clinically indication.
Vital Signs and Oxygen Saturation	X	X		Temperature, BP, HR, RR, O2 saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable) prior to dosing and at any time a subject has any new or worsening respiratory symptoms.
Serious Adverse Event Assessments	X	X		For a minimum of 100 days from the last dose of study therapy, subjects followed for ongoing drug-related adverse events until resolved, symptoms return to baseline, or are deemed irreversible, lost to follow up, or withdrawal of study consent.
Adverse Event Assessments	X	X		For a minimum of 100 days from the last dose of study therapy, subjects followed for ongoing drug-related adverse events until resolved, symptoms return to baseline, or are deemed irreversible, lost to follow up, or withdrawal of study consent.
[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]		[redacted]
Pregnancy Test	----------See notes-----			Every 4 weeks for 6 months following the end of treatment. Completed more frequently if required by local regulations (serum or urine as required by standard of care at the site).
Efficacy Assessments				
Tumor scans	----------See notes----------			Assessments should be performed according to local standards of care or at the investigators discretion and are recommended

Table 5.1-3: CA209171 Off-Treatment Follow Up Assessments				
Procedure	**FU1** **6 weeks (±2 weeks) after last dose**	**FU2** **16 weeks (±2 weeks) after last dose**	**Further Follow-Up** **Every 3 months (±1 month) after FU2**	**Notes**
				every 8-12 weeks. Assessments should include chest, abdomen, and all known or suspected sites of disease.
Survival Follow Up	X	X	X[b]	

[redacted]

[b] In-person visit or telephone call

5.1.1 Retesting During Screening or Lead-in Period

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

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

5.2 Study Materials

The site will provide all required materials for the tests performed locally (ie, relevant to clinical laboratory tests). The site will have available a well-calibrated scale for recording body weight, a calibrated sphygmomanometer, and thermometer for temperature. The site will have a validated temperature-controlled refrigerator. The site will provide all materials required for accurate source documentation of study activities including the Lung Cancer Symptom Scale (LCSS) visual analog scale.

BMS will provide a BMS-approved protocol and any amendments or administrative letters (if required). Case report forms (electronic or hard copy) will be provided by BMS. Nivolumab will be supplied by BMS. BMS will also provide the Investigator Brochure (IB).

5.3 Safety Assessments

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 subject's medical record and should not be provided to BMS unless specifically requested.

Subjects will undergo screening evaluations to determine eligibility as mentioned in Table 5.1-1 prior to first nivolumab dose. Safety, including adverse event monitoring and physical examination, should be monitored continually, and safety assessments are recommended every 2 weeks while receiving nivolumab treatment.

The following assessments should be monitored starting on Cycle 1 Day 1 and will continue as per the schedule in the Time and Events Tables at the specified frequency:

- adverse events continuously throughout the study
- physical examination and physical measurements including weight and ECOG PS
- Complete blood count (CBCs) with differential, including white blood cell (WBC), lymphocyte count, absolute neutrophil count (ANC), hemoglobin, hematocrit, and platelet count. Results to be obtained prior to dosing on infusion days.
- Serum chemistry tests (blood urea nitrogen [BUN] or serum urea level, serum creatinine, sodium, potassium, calcium, chloride, glucose, magnesium, LDH and phosphate). Results to be obtained prior to dosing on infusion days.
- Liver function tests including AST, ALT, total bilirubin, alkaline phosphatase, albumin. Results to be obtained prior to dosing on infusion days.

5.3.1 Imaging Assessment for the Study

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

5.3.2 Vital Signs and Physical Examinations

Vital signs including temperature, blood pressure, heart rate, respiratory rate, oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable) within 72 hours of dosing. Obtain prior to dosing and at any time a subject has any new or worsening respiratory symptoms. If a subject shows changes in oxygen saturation or supplemental oxygen requirement, or other pulmonary-related signs (eg, hypoxia, fever) or symptoms (eg, dyspnea, cough) 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 contained within the Investigator's Brochure.

5.3.3 Pregnancy Testing

Pregnancy testing must be completed for WOCBP at screening, within 24 hours prior to start of study drug (an extension up to 72 hours prior to start of study drug may be permissible in situations where results cannot be obtained within a 24 hour window), every 4 weeks while receiving the program drugs, and every 4 weeks for 6 months following the end of treatment. Pregnancy testing can be completed more frequently if required by local standards. Pregnancy testing may be performed at home if an in-office visit is otherwise not required. Telephone contacts are required to obtain results for all subjects who perform post-treatment at-home pregnancy testing. Although testing may be performed with home pregnancy testing kits, any positive result must be confirmed by serum pregnancy testing at the program site.

5.4 Efficacy Assessments

Mandatory tumor assessments are to be done at Weeks 9 and 52 (±5 days), and additional tumor assessments should be performed as required by local standards of care or at the investigator's discretion as discussed in Table 5.1-2 and are recommended every 8-12 weeks until:

- Disease progression per RECIST 1.1 criteria (or discontinuation of study treatment in subjects receiving nivolumab beyond progression)
- Subject lost to follow-up
- Withdrawal of study consent by subject
- End of study

Study evaluations will take place in accordance with Table 5.1-2 and should be performed according to RECIST 1.1 criteria.

High resolution CT with oral or IV contrast or contrast-enhanced MRI are the preferred imaging modalities for assessing radiographic tumor response. If a subject has a known allergy to contrast material, please use local prophylaxis standards to obtain the assessment with contrast if at all possible or use an alternate modality. In cases where contrast is strictly contraindicated, a non-

contrast scan will suffice. Screening assessments, including chest, abdomen, pelvis, brain, and all known or suspected sites of disease, should be performed within 28 days of first dose of study drug. Brain MRI is the preferred imaging method for evaluating CNS metastasis. In addition to chest and abdomen, all known or suspected sites of disease (including CNS) should be assessed at subsequent assessments using the same imaging method and technique. If more than one method is used at screening, then the most accurate method according to RECIST 1.1 should be used when recording data and should again be used for all subsequent assessments. Bone scan, PET scan, or ultrasound is not adequate for assessment of RECIST response. In selected circumstances where such modalities are the sole modality used to assess certain non-target organs, those non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in the target disease or when progression in bone is suspected. Previously treated CNS metastases are not considered measurable lesions for purposes of RECIST determined response.

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

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

Survival will be followed after progression either by direct contact (office visits) or via telephone contact until death, withdrawal of study consent, lost to follow-up, or end of study.

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6 ADVERSE EVENTS

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

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

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

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

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of 1 or more AEs.)

6.1 Serious Adverse Events

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

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

hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

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

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

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

NOTE:

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

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting.

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur after written consent and up to 100 days of discontinuation of dosing.

The investigator should report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure. All SAEs must be reported from the time of informed consent and up to 100 days after discontinuation of dosing (within 30 days of last visit for enrollment/screening failures).

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

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

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours. 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. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

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

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

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

All SAEs should be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

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

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. 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 the last dose of study treatment.

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

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

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

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

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

6.4 Pregnancy

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

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

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

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours and in accordance with SAE reporting procedures described in Section 6.1.1.

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

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 Overdose

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

6.6 Potential Drug Induced Liver Injury (DILI)

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

Potential drug induced liver injury is defined as:

1) AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)
   AND
2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),
   AND
3) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

6.7 Other Safety Considerations

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

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

The Scientific Steering Committee (SSC) will closely review the safety data throughout the study to provide guidance and scientific expertise on the risk/benefit ratio in general and for the separate prospective subgroups following a predefined Safety Management Plan respecting the data for rate and frequency of Grade 3 and 4 select adverse events (estimated < 25%) and QoL (patient-reported outcomes).

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

The total sample size for this study is based on logistical considerations. Nevertheless, certain statistical properties of the projected sample size are indicated below.

A total of 950 subjects who are evaluated based on the ECOG PS will be enrolled, and a minimum of 11% (95 subjects) should present with PS2. In addition, a minimum of 40% of patients should be enrolled as second-line, and a minimum of 40% of patients should be enrolled as third-line. With a 15% screen failure rate, a total of approximately 800 subjects will be treated. With n = 800

subjects, about 4 subjects will experience a rare adverse event with 0.5% true cumulative event rate within 95% confidence interval (CI) (0.1%-1.3%). Approximately 2 subjects with events and a 95% CI of 0.1%-0.9% for the assumed true event rate of 0.3% are projected. In addition, with 800 subjects, the probability of observing at least one rare event (with 0.25% true rate) is 91.0%.

The 95% CI is calculated using the Clopper-Pearson method in PASS12.

8.2 Populations for Analyses

- All enrolled subjects: all subjects who signed an informed consent form and were registered into the IVRS.
- All treated subjects: all subjects who received any nivolumab. This is the primary population for safety and efficacy analyses. Subpopulation analyses will be conducted by subject PS subgroups.
- All response evaluable subjects: all treated subjects who have baseline and at least one on-study evaluable tumor measurement.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

The primary endpoint is the incidence of high-grade (CTCAE v4.0 Grades 3-4 or higher), treatment-related, select adverse events.

Select adverse events are defined in Section 4.6.1.

8.3.2 Secondary Endpoint(s)

The secondary endpoints include:

- Incidence of high grade (Grade 3-4) select adverse events
- Median time to onset and median time to resolution (Grades 3-4) of select adverse events
- OS is defined as the time from first dosing date to the date of death. A subject who has not died will be censored at last known date alive. OS will be followed continuously while subjects are on treatment and every 3 months via in-person or phone contact after subjects discontinue the study drug.
- ORR is defined as the number and percentage of subjects with a best overall response (BOR) of confirmed CR or PR. ORR as assessed by the investigator will be reported.

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8.4 Analyses

The analysis of primary, secondary (excluding ORR), and exploratory endpoints will be reported for the full safety analysis set, and by subgroups based on ECOG PS. ORR will be reported for the response evaluable analysis set and by PS subgroups.

8.4.1 Demographics and Baseline Characteristics

The demographic characteristics, medical history, and baseline assessments of subjects will be reported as counts and percentages.

Study participation status including completion and discontinuation of treatment will be reported. Reasons for discontinuation will be summarized.

8.4.2 Safety Analyses

Safety data will be presented for all treated subjects and by PS subgroups (PS 0-1 and PS2). In addition, summaries of safety data for subjects randomized to either continue nivolumab monotherapy or discontinue nivolumab monotherapy will also be presented.

8.4.2.1 Primary Analyses

The number and percentage of subjects who report high-grade (Grades 3-4), treatment-related, select adverse events will be summarized for all treated subjects and by subgroups. Treatment-related, select adverse events will be tabulated using worst grade per NCI CTCAE V4.0 criteria by system organ class (SOC) and Medical Dictionary for Regulatory Affairs (MedDRA) preferred terms.

In addition to reporting number and percentages of subjects with select adverse events, 95% CIs for incidence density rates will be provided based on the Poisson distribution.

8.4.2.2 Secondary Analyses

The number and percentages of subjects who report high-grade (Grades 3-4) select adverse events, regardless of relationship to treatment, will be summarized for all treated subjects by subgroups and randomized subjects. Select adverse events will be tabulated using worst grade per NCI CTCAE V4.0 criteria by SOC and MedDRA preferred terms. In addition to reporting number and percentages of subjects with select adverse events, 95% confidence intervals (CIs) for incidence density rates will be provide based on the Poisson distribution

In addition, descriptive statistics for time to onset and time to resolution of select adverse events will be estimated using Kaplan-Meier (KM) product limit method for all treated subjects and by subgroups. Median time to onset and median time to resolution, if estimable, will be presented together with their 95% CI using Brookmeyer and Crowley method. If medians are not estimable, other percentiles (eg, 10th or 25th) may be reported.

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8.4.3 Efficacy Analyses

OS is defined as the time between the start of treatment and the date of death due to any cause. A subject who has not died will be censored at last known date alive. OS will be followed up while subjects are on the study drug and every 3 months via in-person or phone contact after subjects discontinue the study drug.

OS will be summarized using Kaplan-Meier (KM) product-limit method and associated statistics for the treated analysis set. Median values of OS, if estimable, along with 2-sided 95% CI using the Brookmeyer and Crowley method will be calculated. If medians are not estimable, other percentiles (eg, 10th and 25th) may be reported. OS rates at selected time points, including survival rates at Years 1 and 2, together with their 95% CIs will also be estimated using KM estimates on the OS curves. Associated 2-sided 95% CIs will be calculated using the Greenwood formula. OS summary statistics indicated earlier for the treated analysis set will be reported by subgroups.

The ORR will be summarized by binomial response rates and their corresponding two-sided 95% exact CIs using the Clopper-Pearson method. This analysis will be performed for all response evaluable subjects. This analysis will also be performed by subject subgroups.

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9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC and Regulatory Authority(ies), if required by local regulations, of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

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

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

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

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

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

9.1.2 Monitoring

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

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

9.1.2.1 Source Documentation

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

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

9.1.3 Investigational Site Training

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

9.2 Records

9.2.1 Records Retention

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

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

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

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of study drug (inventoried and dispensed) is maintained at the study site to include investigational product.

Records or logs must comply with applicable regulations and guidelines and should include the following:

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

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

9.2.3 Case Report Forms

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

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paper or electronic SAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

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

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

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form .For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

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

9.3 Clinical Study Report and Publications

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

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

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee
- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study require approval by BMS prior to publication or presentation and must adhere to BMS's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to BMS at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. BMS shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	If 1 form of contraception is required, Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. If 2 forms of contraception are required, complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. **Expanded definition** Complete abstinence as defined as complete avoidance of heterosexual intercourse is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (e.g., calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence

11 LIST OF ABBREVIATIONS

Term	Definition
AE	Adverse event
AEOSI	Adverse events of special interest
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
APC	Antigen-presenting cells
ANC	Absolute neutrophil count
BMS	Bristol-Myers Squibb
BOR	Best overall response
BP	Blood pressure
BUN	Blood urea nitrogen
CBC	Complete blood count
CR	Complete response
CRC	Colorectal carcinoma
CrCl	Creatinine Clearance
CRPC	Castrate-resistant prostrate carcinoma
CT	Computed tomography
CTCAE	Common Terminology Criteria for AEs
DILI	Drug-induced liver injury
EAP	Expanded access program
ECOG	Easter Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EGFR-TKI	Epidermal growth factor receptor-tyrosine kinase inhibitor
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
HCV Ab	Hepatitis C antibody
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus

Term	Definition
HRT	Hormone replacement therapy
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IUD	Intrauterine device
IVRS	Interactive voice response system
KM	Kaplan Meier
LCSS	Lung Cancer Symptom Score
LDH	Lactate dehydrogenase
mPFS	Median progression-free survival
LFT	Liver function test
MRI	Magnetic Resonance Imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
O2	Oxygen
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed cell death - 1
PR	Partial response
PFS	Progression-free survival
PRO	Patient-reported outcomes
PS	Performance status
QoL	Quality of life
PT	Preferred terms
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RR	Respiratory rate
SSC	Scientific Steering Committee
SqNSCLC	Squamous cell non-small cell lung cancer
TFT	Thyroid function test
TSH	Thyroid stimulating hormone

Term	Definition
ULN	Upper limit of normal
WBC	White blood cell
WOCBP	women of childbearing potential