Protocol Number: CA209172
IND Number: NA
EUDRACT Number 2014-001286-28
Date: 18-Apr-2014
Revised Date 17-Nov-2017

Clinical Protocol CA209172

A Single-Arm, Open-Label, Multicenter Clinical Trial with Nivolumab (BMS-936558) for Subjects with Histologically Confirmed Stage III (unresectable) or Stage IV Melanoma Progressing After Prior Treatment Containing an Anti-CTLA-4 Monoclonal Antibody

CheckMate 172: **CHECK**point pathway and nivolu**MA**b clinical **T**rial **E**valuation 172

Revised Protocol 06
Incorporates Amendment 08 and Administrative Letter 06

Study Director

Elena Grigoryeva, MD, PhD

[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 06	17-Nov-2017	Incorporates Amendment 08 and Administrative Letter 06
Amendment 08	17-Nov-2017	Changed the duration of follow-up from 5 years to 2 years after the first dose of study drug treatment due to a decision to close the study in 2018. This decision was based on adequate safety data obtained since the study's opening in 2014, which are consistent with the known safety profiles of the study drugs.
Administrative Letter 06	25-Jan-2017	Changed MM Address
Revised Protocol 05	08-Dec-2015	Incorporates Amendment 06
Amendment 06	08-Dec-2015	Adds dosing windows to the Time and Events Schedule
Revised Protocol 04	28-Oct-2015	Incorporates Administrative Letter 05 and Amendment 05
Amendment 05	28-Oct-2015	• To provide further clarity on the requirements for lipase testing • To provide clarity on dose calculations • To allow the EQ-5D-3L to be completed without an office visit if one is not otherwise needed.
Administrative Letter 05	23-Jul-2015	• The of expectations when lipase results are not available prior to dosing • Aligning the footnotes of Table 5.1-2 and Section 5.3, Safety Assessments with the requirements for lipase described in Table 5.1-2. • Assessments allowed to be done according to standard of care • At what cycle assessments should start and assessment windows • When RECIST 1.1 criteria must be used. NOTE: Administrative Letter 04 was not finalized because it was considered to not be needed. However, Administrative Letter 05 was created and finalized with the mistaken understanding that Administrative Letter 04 was finalized.
Revised Protocol 03	02-Jun-2015	Incorporates Amendment 04
Amendment 04	02-Jun-2015	Decreases sample size
Revised Protocol 02	19-Mar-2015	Incorporates Amendment 03
Amendment 03	19-Mar-2015	This Amendment removes the inclusion of the treatment-naïve patients, also referred to as the first-line cohort.
Revised Protocol 01	16-Jan-2015	Incorporates Amendment 02 and Administrative Letter 03.
Amendment 02	16-Jan-2015	• The inclusion criteria have been expanded and the exclusion criteria have been minimized. • The study rationale also offers greater support for the expanded

Document	Date of Issue	Summary of Change
		subject population. • Treatment-naïve patients have been added. • The options for palliative local therapy have also been expanded to meet the needs of the current patient populations. • The EORTC QLQ-C30 has been eliminated from the patients' follow up. • The time points and frequency of assessments have been updated. • The subjects in Cohort 2 will now be analyzed at the same frequency to Cohort 1, so the separate Time and Events Schedule for Cohort 2 was removed. • The statistical section has been reformatted to aid understanding of the analyses to support the respective primary, secondary, [redacted] objectives. • The timing and frequency of all assessments have been removed from sections of the protocol outside of the Time and Events tables. • The endpoints are more representative of the data that will be collected in support of the objectives. • The requirement for electrocardiograms has been removed.
Administrative Letter 03	02-Oct-2014	Correct the tables in Section 5.1, Flow Chart/Time and Events Schedule so that the information in these tables is consistent with the text in the protocol.
Revised Protocol 01a	04-Jun-2014	Incorporates Administrative Letter 01, Administrative Letter 02, and Amendment 01.
Amendment 01	04-Jun-2014	Revisions aim to comply with the Health Authority requirements in Germany
Administrative Letter 02	21-May-2014	A number was missing from Exclusion Criterion 4cviii. This letter is to provide you with the missing number. This is an administrative protocol change and does not significantly affect the safety of subjects, study scope, or scientific quality of a Phase IIb. Accordingly, it may be implemented immediately.
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. This is an administrative protocol change and does not significantly affect the safety of subjects, study scope, or scientific quality of a Phase II or III protocol. Accordingly, it may be implemented immediately.
Original Protocol	18-Apr-2014	Not applicable

SYNOPSIS

Clinical Protocol CA209172

Protocol Title: A Single-Arm, Open-Label, Multicenter Clinical Trial with Nivolumab (BMS-936558) for Subjects with Histologically Confirmed Stage III (unresectable) or Stage IV Melanoma Progressing After Prior Treatment Containing an Anti-CTLA-4 Monoclonal Antibody **C**heck**M**ate **172**: **CHECK**point pathway and nivolu**MA**b clinical **T**rial **E**valuation 172

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 for a maximum of 24 months

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 patients with histologically-confirmed, stage III (unresectable) or stage IV melanoma treated and progression after prior treatment containing an anti-CTLA-4 monoclonal antibody with nivolumab monotherapy.

Objectives:

The primary objective of this trial is to determine the incidence of high-grade (CTCAE v4.0 Grade 3 or higher), treatment-related, select adverse events in patients with histologically confirmed stage III (unresectable) or stage IV melanoma and progression after prior treatment containing an anti-CTLA-4 monoclonal antibody.

The secondary objectives of this study are:

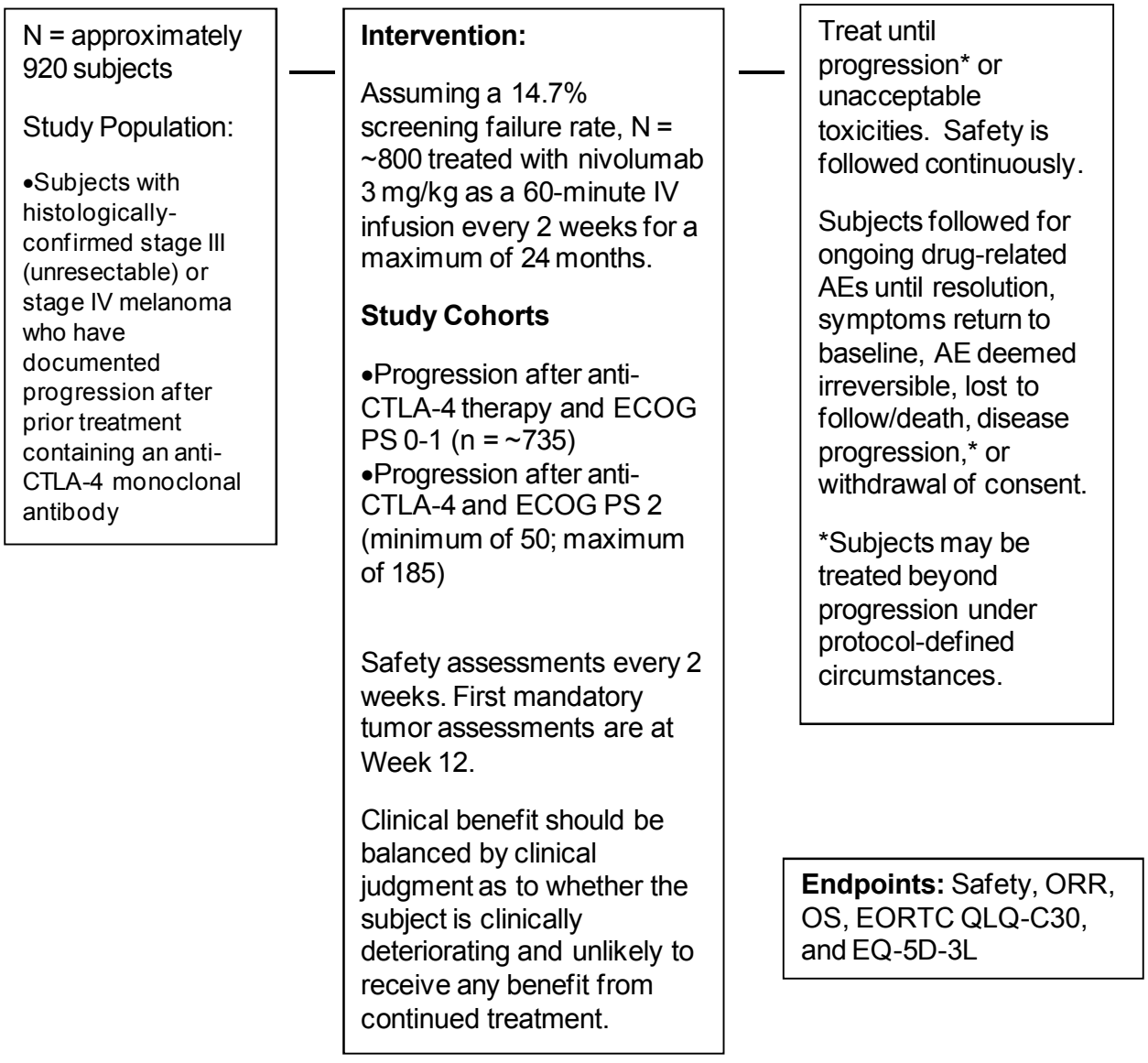
- To determine the incidence and to characterize the outcome of all high-grade (CTCAE v4.0 Grade 3 or higher), select adverse events in patients with histologically confirmed stage III (unresectable) or stage IV melanoma and progression after prior treatment containing an anti-CTLA-4 antibody, treated with nivolumab monotherapy.
- To estimate overall survival (OS) in all treated subjects
- To estimate Investigator-assessed objective response rate (ORR)

[redacted]

Study Design: The study will include patients with histologically-confirmed stage III (unresecteable) or stage IV advanced melanoma who have documented progression after treatment containing an anti-CTLA-4 monoclonal antibody. Patients will be treated with 3 mg/kg of nivolumab IV every 2 weeks for a maximum of 24 months. Patients will undergo screening evaluations to determine eligibility within 6 weeks prior to first dose following the signing of an informed consent. Each 14-day dosing period will constitute a cycle.

The Scientific Steering Committee will evaluate the clinical risk/benefit ratio closely following a defined Safety Management Plan.

Study Schematic:



Study Population:

Key inclusion criteria:

Patients with progression after prior treatment containing an anti-CTLA-4 monoclonal antibody (Cohorts 1 and 2):

a) Patients with histologically confirmed malignant melanoma
b) Eastern Cooperative Oncology Group (ECOG) Performance Status (PS):

i) PS 0 to 1 (Cohort 1)

ii) PS 2 (Cohort 2; a minimum of 50 patients and maximum of 185; clinical risk benefit ratio of Cohort 2 will be monitored by the Scientific Steering Committee)

c) Previously treated unresectable stage III or stage IV melanoma as per the American Joint Committee on Cancer 2010 Guidelines regardless of BRAF mutation status

d) Patients must have experienced disease progression or recurrence after prior treatment containing an anti-CTLA-4 monoclonal antibody

e) Prior treatment with chemotherapy, interferon (adjuvant setting), IL-2, BRAF/MEK inhibitors for subjects with known BRAF mutations, MEK inhibitors for NRAS mutations, and cKIT inhibitor subjects with known cKIT mutations are allowed

f) Patients with CNS metastases:

i) Patients 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 enrollment. In addition, patients must be either off corticosteroids or on a stable or decreasing dose ≤10 mg daily prednisone (or equivalent)

OR

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

OR

iii) Patients with additional leptomeningeal metastases are eligible if they are treated and neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to enrollment and have a life expectancy of at least 3 months. In addition, subjects must be either off corticosteroids or on a stable or decreasing dose of ≤10 mg daily prednisone (or equivalent)

g) Patients must have evaluable disease by CT or MRI per RECIST 1.1 criteria (radiographic tumor assessment performed within 6 weeks of first dose of study drug) or clinically apparent disease that the investigator can follow for response.

Key exclusion criteria:

h) Subjects with untreated, symptomatic CNS metastases 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 CA209172		
Medication	**Potency**	**IP/Non-IP**
Nivolumab Injection BMS-936558-01a	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 patient'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 Table at the specified frequency until discontinuation from study therapy:

- Adverse events continuously throughout the study
- Physical examination and physical measurements including weight and ECOG PS

- Complete blood count with differential, including white blood cells, lymphocyte count, absolute neutrophil count, hemoglobin, hematocrit, and platelet count. Results to be obtained prior to dosing on infusion days.
- Serum chemistry tests (blood urea nitrogen or serum urea level, serum creatinine, sodium, calcium, phosphate, chloride, glucose, lipase, and lactate dehydrogenase). Results to be obtained prior to dosing on infusion days. Amylase should be performed in addition to lipase in cases where lipase results are not available prior to dosing.
- Liver function tests including aspartate aminotransferase, alanine transaminase total bilirubin, alkaline phosphatase, and albumin. Results to be obtained prior to dosing on infusion days.
- Thyroid function testing includes thyroid stimulating hormone (free T3 and free T4 if abnormal results for TSH)

During the 100 days after the last dose of the study treatment, patients will have 2 additional follow up visits to assess safety.

Efficacy assessments include initial mandatory tumor assessments at Week 12 (± 5 days). Further tumor assessments should be completed as required by local standards of care or at the investigator's discretion and are recommended every 8 weeks.

Changes in tumor measurements and tumor responses to guide ongoing study treatment decisions should be assessed by the investigator using RECIST 1.1.

Per Amendment 08, the EQ-5D-3L and survival follow up will be collected for up to 2 years from the first dose of study therapy or until death, withdrawal of study consent, or lost-to-follow-up as indicated in the assessment table.

Statistical Considerations:

Sample Size: With an approximate 15% screening failure rate, a cohort of 735 screened PS1 patients is projected to a yield 640 treated patients. With n = 640 patients, about 3 will experience a rare adverse event with 0.5% true cumulative event rate with a rate estimated within 95% confidence interval (CI) (0.2%-1.1%). Approximately 2 patients with events and a 95% CI of (0%-1.1%) for assumed true event rate of 0.3% are projected.

Endpoints: The primary endpoint is the incidence for high-grade (CTCAE v4.0 Grade 3 or higher), treatment-related, select adverse events.

The secondary endpoints include:

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

[redacted]

Analyses: The evidence for the research hypothesis of this clinical trial that high-grade (CTCAE v4.0 Grade 3 or higher), treatment-related select adverse events occur with a low frequency in patients with advanced (unresectable or metastatic) melanoma will be presented in terms of the number, percentage of subjects, and 95% confidence interval for the percentage with these select adverse events during treatment and off-treatment overall and by cohort.

Adverse events from date of enrollment up to last contact with patients will be presented for the full study duration and separately for events that occur on- or post-treatment. In particular, safety data will be summarized and listed for all treated patients using the NCI CTCAE version 4.0. All on-study AEs, drug-related AEs, SAEs, and drug-related SAEs will be tabulated using worst grade per NCI CTCAE v4.0 criteria by system organ class and MedDRA preferred term. On-study laboratory parameters including hematology, chemistry, liver function, thyroid function, and renal function will be summarized using worst grade per NCI CTCAE v4.0 criteria.

Overall survival 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 summarized using Kaplan-Meier (KM) product-limit method and associated statistics. Median values of OS, if estimable, along with 2-sided 95% CI using the Brookmeyer and Crowley method will be calculated. Overall survival 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 by cohorts and subgroups will also be reported. OS will be further presented by initial investigator-assessed objective response under treatment with an anti-CTLA-4 monoclonal antibody.

ORR is defined as the number and percentage of patients with a best overall response (BOR) of confirmed CR or PR. ORR as assessed by the investigator will be reported.

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1.4 Product Development Background

1.4.1 Clinical Activity of Nivolumab

Efficacy with Nivolumab

In CA209003, the clinical activity of nivolumab was demonstrated in a variety of tumor types and across a range of doses (0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg). As of the clinical cut-off date of 05-Mar-2013, a total of 306 subjects with melanoma, RCC, and NSCLC have been treated with nivolumab. All subjects initiated treatment at least one year prior to analysis. A response of either CR or PR, as determined by investigator-assessed tumor evaluations based on modified RECIST 1.0, has been reported at all dose levels.

Among 107 patients with advanced melanoma who received nivolumab, the preliminary objective response rate was 33/107 (31%). Responses occurred at each dose level, with 6/17 (35%), 5/18 (28%), 11/35 (31%), 7/17 (41%), and 4/20 (20%) melanoma subjects responding at 0.1, 0.3, 1, 3, and 10 mg/kg, respectively. Duration of response ranges from 24.1 to 48.7+, 18.4 to 66.3+, 32.4 to 108.1+, 40.1+ to 115.4+, and 73.9 to 117.0+ months in melanoma subjects treated at 0.1, 0.3, 1, 3, and 10 mg/kg, respectively. An additional 7% of melanoma subjects had stable disease for 24 weeks or longer. More importantly, across dose levels, melanoma subjects achieved a median overall survival of 16.8 months (95% CI: 12.5, 31.6), with a 1- and 2-year overall survival rate of 62% and 43%, respectively, which are favorable as compared with those reported in the literature in similar patient populations. Furthermore, 47 patients are still alive with a median overall follow-up of 22 months and a range of 14 to 51 months.

There are 4 trials in the clinical development program looking at the activity of nivolumab in first-line (1L), second-line (2L), and third-line (3L) advanced melanoma.

- CA209-037: 2-arm Phase 3 study of nivolumab vs investigator's choice in ipilimumab previously-treated melanoma patients (N=390)
- CA209-066 (ex-US pivotal study): 2-arm Phase 3 study of nivolumab vs DTIC in previously-untreated, unresectable or metastatic BRAF wild-type melanoma (N=410)
- CA209-067: 3-arm Phase 3 study of nivolumab or nivolumab + ipilimumab vs ipilimumab in previously-untreated, unresectable or metastatic melanoma (N=915)
- CA209-069: 2-arm Phase 2 study of nivolumab + ipilimumab vs ipilimumab in previously untreated, unresectable or metastatic melanoma (N= 120)

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

1.4.1.1 Clinical Activity in Sequential Administration of Nivolumab After Ipilimumab (CA209-004)

Additionally, a Phase Ib study CA209-004, A Phase 1b, Open-label, Multicenter, Multidose, Dose-Escalation Study of Nivolumab (BMS936558; MDX-1106) in Combination with Ipilimumab in Subjects with Unresectable Stage III or Stage IV Malignant Melanoma, primarily investigated safety and tolerability of the combination and sequential approach of ipilimumab and nivolumab.[32] A total of 86 patients were treated. Fifty-three patients received the concurrent regimen, and 33 received the sequenced regimen. Most patients (73%) enrolled in the sequenced-regimen cohorts had progression as assessed radiographically during prior treatment with ipilimumab. In the sequenced-regimen cohorts, 6 of 30 patients (20%; 95% CI, 8 to 39) had an objective response, including 1 with a complete response. A total of 4 patients (13%) had tumor reduction of 80% or more at 8 weeks. An additional 6 patients had either an immune-related response (in 3 patients) or an unconfirmed response. When clinical activity was defined by objective, immune-related, or unconfirmed responses or stable disease for at least 24 weeks, 43% of patients (95% CI, 26 to 63) in the sequenced-regimen group had clinical activity. Some patients who had not had a response to previous treatment with ipilimumab did have a response to subsequent treatment with nivolumab. These data indicate the potential benefit of sequential administration of nivolumab after progression during or after ipilimumab treatment.

The most advanced and robust data coming from the Phase III randomized clinical study (CA209037) versus chemotherapy of investigator's choice have been presented at the European Society of Medical Oncology 2014 annual meeting.[33] In total, 272 patients have been treated with nivolumab who have progressed following ipilimumab. The co-primary endpoint of objective response rate was assessed in the first 120 nivolumab-treated subjects that had a minimum of 6 months follow-up. The confirmed ORR by RECIST 1.1 criteria by central review was 32% vs 11% in the chemotherapy cohort. This included 3% complete responses vs 0% CRs in the nivolumab and investigator's choice arm, respectively. The majority of responses (95%) were ongoing in patients who received nivolumab, and the medial duration of response was not reached while the median duration of response was 3.6 months in the investigator's choice arm. The Responses were

observed regardless of pre-treatment, PD-L1 expression status, BRAF mutation status, and prior ipilimumab benefit.

1.4.2 Adverse Effects with Nivolumab Therapy

Two studies have contributed to most of the monotherapy clinical experience with nivolumab in subjects with melanoma and other solid malignancies. CA209001 was a Phase 1 single-dose dose escalation study in 39 subjects with previously treated advanced or metastatic cancer. Subjects received a single dose of nivolumab at 0.3, 1, 3, or 10 mg/kg with an option for retreatment at 3 months. CA209003 is an ongoing Phase 1 open-label, multiple dose escalation study in 304 subjects with select previously treated advanced solid tumors, including melanoma, RCC, NSCLC, colorectal cancer, and hormone-refractory prostate cancer. Subjects received nivolumab at doses of 0.1, 0.3, 1, 3 or 10 mg/kg intravenously every 2 weeks, up to a maximum of 2 years of total therapy. As of 03-Jul-2012, a total of 107 melanoma subjects were treated with nivolumab in the dose range of 0.1-10 mg/kg.

Adverse Events

Treatment-related AEs were reported in 230 (75.2%) of the 306 patients in the CA209003 study. The most frequently reported treatment-related AEs were fatigue (28.1%), rash (14.7%), diarrhea (13.4%), and pruritus (10.5%) (Table 1.4.2-1). Of the AEs, most were low-grade (Grade 1 to Grade 2) with relatively few related high-grade (Grade 3 to Grade 4) AEs reported in 52 (17.0%) patients. The most frequently reported treatment-related, high-grade AE was fatigue (6.5%). Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies).

The one exception is pulmonary inflammation AEs, which may be numerically greater in patients with NSCLC because, in some cases, it can be difficult to distinguish between nivolumab-related and unrelated causes of pulmonary symptoms and radiographic changes.

Due to the immune mechanism of action of nivolumab, there are select AEs that require more frequent monitoring and/or unique intervention, such as immunosuppression. These adverse events of special interest (AEOSIs) include GI AEs, pulmonary AEs, renal AEs, hepatic AEs, skin AEs, endocrinopathies, and infusion reactions. Each category is composed of a discrete set of preferred terms, and AE management algorithms have been developed for suspected pulmonary toxicity, diarrhea or suspected colitis, hepatotoxicity, endocrinopathy, and nephrotoxicity. These may be found in the investigators brochure for nivolumab.

Three patients in CA209003 (one with colorectal carcinoma and two with NSCLC) died after developing pneumonitis. There was no clear relationship between the occurrence of pneumonitis and tumor type, dose level, or the number of doses received. Early grade pneumonitis was generally reversible with treatment discontinuation and corticosteroid administration. Several patients in these categories successfully reinitiated treatment with nivolumab. There were seven patients with treatment-related SAEs; of these, 4 patients had Grade 3-4 SAEs in CA209003.

Table 1.4.2-1: Summary of Adverse Events Reported in 15% of All Treated Subjects - CA209003

Preferred Term	No. of Subjects (%)			
	AEs regardless of causality		Treatment-related AEs	
	Any Grade N=306	Grade 3-4 N=306	Any Grade N=306	Grade 3-4 N=306
Any AE	303 (99)	127 (42)	230 (75)	52 (17)
Fatigue	168 (55)	20 (7)	86 (28)	7 (2)
Decreased appetite	107 (35)	3 (1)	28 (9)	1(0.3)
Diarrhea	105 (34)	3 (1)	41 (13)	3 (1)
Nausea	92 (30)	9 (3)	27 (9)	2 (1)
Cough	90 (29)	4 (1)	11 (4)	1 (0.3)
Dyspnea	80 (26)	27 (9)	11 (4)	0
Constipation	78 (26)	2 (1)	5 (2)	0
Rash	74 (24)	0	45 (15)	0
Vomiting	70 (23)	7 (2)	10 (3)	1 (0.3)
Back pain	68 (22)	7 (2)	3 (1)	1 (0.3)
Arthralgia	63 (21)	4 (1)	15 (5)	0
Pyrexia	61 (20)	1 (0.3)	17 (6)	0
Headache	59 (19)	1 (0.3)	8 (3)	0
Oedema peripheral	59 (19)	1 (0.3)	3 (1)	0
Dizziness	56 (18)	1 (0.3)	10 (3)	0
Pruritus	56 (18)	1 (0.3)	32 (11)	1 (0.3)
Weight decreased	48 (16)	1 (0.3)	11 (4)	0
Malignant neoplasm progression	48 (16)	4 (1)	1 (0.3)	1 (0.3)

Abbreviations: AE: adverse event. Source: Preliminary data, CA209003. Clinical data cut-off date: 18-Mar-2013.

Serious Adverse Events

Treatment-related Grade 3-4 SAEs reported in at least 2 patients included pneumonitis (4 patients, 1.3%), diarrhea (3 patients, 1.0%), lipase increased (2 patients, 0.7%), pneumonia (2 patients, 0.7%), and hypersensitivity (2 patients, 0.7%). Two patients treated with 1 and 10 mg/kg nivolumab died due to sepsis related to study treatment.

Adverse Events Leading to Discontinuation

At least 1 treatment-related AE leading to discontinuation was reported in 32 (10.5%) of the 306 treated patients. The frequency of treatment-related AEs leading to discontinuation was not associated with the dose of nivolumab.

Pneumonitis was the most common treatment-related AE leading to discontinuation (8 patients, 2.6%); pneumonitis, reported in 3 (1.0%) patients, was Grade 3-4. Treatment-related AEs reported in ≥2 patients included: pneumonitis (8 patients, 2.6%), colitis (3 patients, 1.0%) and myalgia, hepatitis, hypersensitivity, and infusion-related reactions (each reported in 2 patients, 0.7%).

Deaths

As of 18-Mar-2013, 195 deaths have been reported in CA209003 during the course of the study or within 30 days of last dose of study drug. The majority of the deaths were considered secondary to disease progression and malignant disease.

Three patients in CA209003 died after developing pneumonitis thought to be related to the study drug. A 62-year-old male with NSCLC (adenocarcinoma) in the 1 mg/kg treatment group and a 59-year old-male with CRC in the 10 mg/kg treatment group both died due to Grade 5 sepsis after developing Grade 4 pneumonitis.

The sepsis and pneumonitis were considered related to study drug by the investigator in both of these cases.

Additional deaths reported as due to "other" in CA209003 included:

- Patient on dose (10 mg/kg): Ischemic cardiomyopathy
- Patient on dose (10 mg/kg): Death caused by superior mesenteric vein thrombosis
- Patient on dose (1 mg/kg): Progressive lung cancer

Laboratory Abnormalities

Among all treated patients in CA209003 (N=306), laboratory test results with shifts greater than 2 grades from baseline value were reported for absolute neutrophils, ALT, creatinine, hemoglobin, leukocytes, lymphocytes, platelet count, and total bilirubin (Table 1.4.2-2). There were no dose-related patterns with regard to frequency or severity. Laboratory value changes were recorded regardless of causality and may not correlate with reported laboratory-based AEs.

Table 1.4.2-2: Summary of Select Laboratory Test Results with Shifts Greater Than 2-Grades From Baseline Value - Patients (%)

Laboratory Test	Laboratory Shifts	Total Treated (N=306)
ALT	Grade 0 to 2	10 (3.3)
	Grade 0 to 3	4 (1.3)
AST	Grade 0 to 2	9 (2.9)
	Grade 0 to 3	6 (2.0)
	Grade 2 to 4	1 (0.3)
Bilirubin, Total	Grade 0 to 2	3 (1.0)
	Grade 0 to 3	2 (0.7)
	Grade 0 to 4	1 (0.3)

Table 1.4.2-2: Summary of Select Laboratory Test Results with Shifts Greater Than 2-Grades From Baseline Value - Patients (%)

Laboratory Test	Laboratory Shifts	Total Treated (N=306)
Creatinine	Grade 1 to 3	1 (0.3)
	Grade 0 to 2	4 (1.3)
Hemoglobin	Grade 1 to 3	1 (0.3)
	Grade 0 to 2	11 (3.6)
Lymphocytes	Grade 0 to 3	2 (0.7)
	Grade 1 to 3	5 (1.6)
	Grade 2 to 4	1 (0.3)
	Grade 0 to 2	17 (5.6)
	Grade 0 to 3	1 (0.3)
	Grade 0 to 4	1 (0.3)
Neutrophils	Grade 1 to 3	14 (4.6)
	Grade 2 to 4	3 (1.0)
	Grade 0 to 2	9 (2.9)
	Grade 0 to 3	4 (1.3)
	Grade 0 to 4	1 (0.2)
Platelet count	Grade 0 to 2	4 (1.3)
Leukocytes	Grade 0 to 2	15 (4.9)
	Grade 0 to 3	4 (1.3)

Abbreviations: ALT: alanine aminotransferase, AST: aspartate aminotransferase

1.4.3 Safety Aspects in Sequential Administration of Nivolumab After Ipilimumab (CA209-004):

Among the 33 patients in the sequenced-regimen group of the Phase Ib study investigating the combination/sequence of nivolumab plus ipilimumab or nivolumab after ipilimumab, adverse events of any grade, regardless of attribution, were observed in 29 patients (88%). Treatment-related adverse events were observed in 24 patients (73%), with the most common events including pruritus (in 18% of patients) and elevated lipase levels (in 12%). Grade 3 or 4 adverse events, regardless of whether they were attributed to the therapy, were observed in 11 patients (33%), and Grades 3 or 4 adverse events related to therapy were observed in 6 (18%) with an elevated lipase level as the most common event (in 6% of patients). Serious adverse events related to therapy were reported in 7 patients (21%). Grade 3 or 4 endocrine events were noted as treatment-related selected adverse events in 2 patients. One patient had Grade 2 pneumonitis. Three patients (9%) discontinued therapy owing to treatment-related adverse events.[34]

The most advanced safety data coming from the Phase III randomized clinical study (CA209037) versus chemotherapy of investigator's choice have been presented at the European Society of Medical Oncology 2014 annual meeting.[35]

In total 268 patients treated with Nivolumab and 102 patients treated with chemotherapy of investigator´s choice have been analyzed for safety. 9% (24) of the patients in the Nivolumab arm have experienced drug-related grade 3 and 4 AEs, while 31% (32) of the patients in the chemotherapy arm have experienced grade 3 and 4 AEs. This was leading to 2% (6) of the patients in the Nivolumab arm and 8% (8) in the chemotherapy arm to discontinue treatment due to drug-related adverse events.

All grade 3-4 drug-related AEs in the Nivolumab arm, belonging to the select AE categories resolved and in total, less than 5% of patients treated with Nivolumab reported Grade 3–4 select AE.

1.5 Overall Risk/Benefit Assessment

Patients with advanced (unresectable) stage III or metastatic stage IV melanoma progressing after treatment containing an anti-CTLA-4 monoclonal antibody represent a clear unmet medical need. Vermurafenib, dabrafenib, and trametinib are approved agents for patients who harbor BRAF mutations and can confer RECIST 1.1 criteria clinical response rates > 50%. Nevertheless, the responses are almost all short lived; median duration for BRAF inhibitors in multiple clinical trials has been approximately 5 months, and the overwhelming majority of patients develop disease progression within 1 year.

Beyond these agents, no other EMA-approved therapy has demonstrated a median overall survival benefit in advanced melanoma patients in a Phase 3 randomized study. The clinical activity of nivolumab observed to date in melanoma suggests the potential for improved clinical outcomes, including survival, as monotherapy. Nivolumab has the potential for clinically relevant adverse events including events with a potential inflammatory mechanism, which may necessitate immunosuppressant intervention and/or endocrine replacement therapy. The most common AEs included fatigue, rash, pruritus, diarrhea, and nausea. Other AEs associated with nivolumab may include those that are GI, pulmonary, renal, hepatic, skin, endocrinopathies, or infusion reactions.

However, the activity and manageable AE profile observed with nivolumab supports a clinical trial in subjects with histologically confirmed stage III (unresectable) or stage IV melanoma progressing after prior treatment containing an anti-CTLA-4 monoclonal antibody for a better understanding of the safety profile in a Pan-European Clinical Trial and in formerly excluded patient populations.

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

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

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

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

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

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

2.2 Institutional Review Board/Independent Ethics Committee

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

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

2.3 Informed Consent

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

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

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

Investigators must:

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.

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 patients with histologically-confirmed stage III (unresectable) or stage IV advanced melanoma who have documented progression after treatment containing an anti-CTLA-4 monoclonal antibody. Patients will be treated with 3 mg/kg of nivolumab IV every 2 weeks for a maximum of 24 months. Patients will undergo screening evaluations to determine eligibility within 6 weeks prior to the first dose following the signing of an informed consent. Each 14-day dosing period will constitute a cycle.

The Scientific Steering Committee will evaluate the clinical risk/benefit ratio closely following a defined Safety Management Plan.

Patients will undergo screening evaluations to determine eligibility as indicated in Table 5.1-1 prior to first dose following signed informed consent. Patient's demographic data will be collected: date of birth, gender, disease stage, date of diagnosis, previous treatments, comorbidities,

performance status, lactate dehydrogenase (LDH) level, type of melanoma (mucosal, uveal), and mutation status if known (BRAF, NRAS, cKIT).

Safety, including adverse event monitoring and physical examination, should be monitored continually, and safety assessments are discussed in Table 5.1-2.

Mandatory initial tumor assessments are to be done at Week 12 (± 5 days). Further tumor assessments should be performed according to institutional standard of care and are recommended every 8 weeks until:

- disease progression
- a concurrent malignancy requires treatment
- the patient is lost to follow up
- the patient withdraws study consent
- completed 24 months of treatment

Patients will not be permitted to continue their treatment beyond initial Investigator-assessed progressive disease unless they meet the following criteria:

- Investigator-assessed clinical benefit
- Patient is tolerating study drug

The investigator should use his or her clinical judgment to assess clinical benefit by considering whether the patient is clinical deteriorating and unlikely to receive any benefit from continued treatment with nivolumab.

Per Amendment 08, follow up begins when the decision to discontinue a patient from study therapy is made (no further treatment with nivolumab) and continues from first dose of study therapy up to 2 years or until death, withdrawal of study consent, or lost-to-follow-up.

The cohorts are described in Table 3.1-1.

Table 3.1-1: Patient Cohorts

(Cohort Number)	Disease Criteria
Cohort 1: Advanced Melanoma (unresectable stage III or stage IV) (N >735)	• ECOG Performance Status 0 to 1 • Progressing after prior therapy containing treatment with an anti-CTLA-4 monoclonal antibody
Cohort 2: Advanced Melanoma (unresectable stage III or stage IV) (N ≥ 50 but ≤ 185)	• ECOG Performance Status 2 • Progressing after prior therapy containing treatment with an anti-CTLA-4 monoclonal antibody

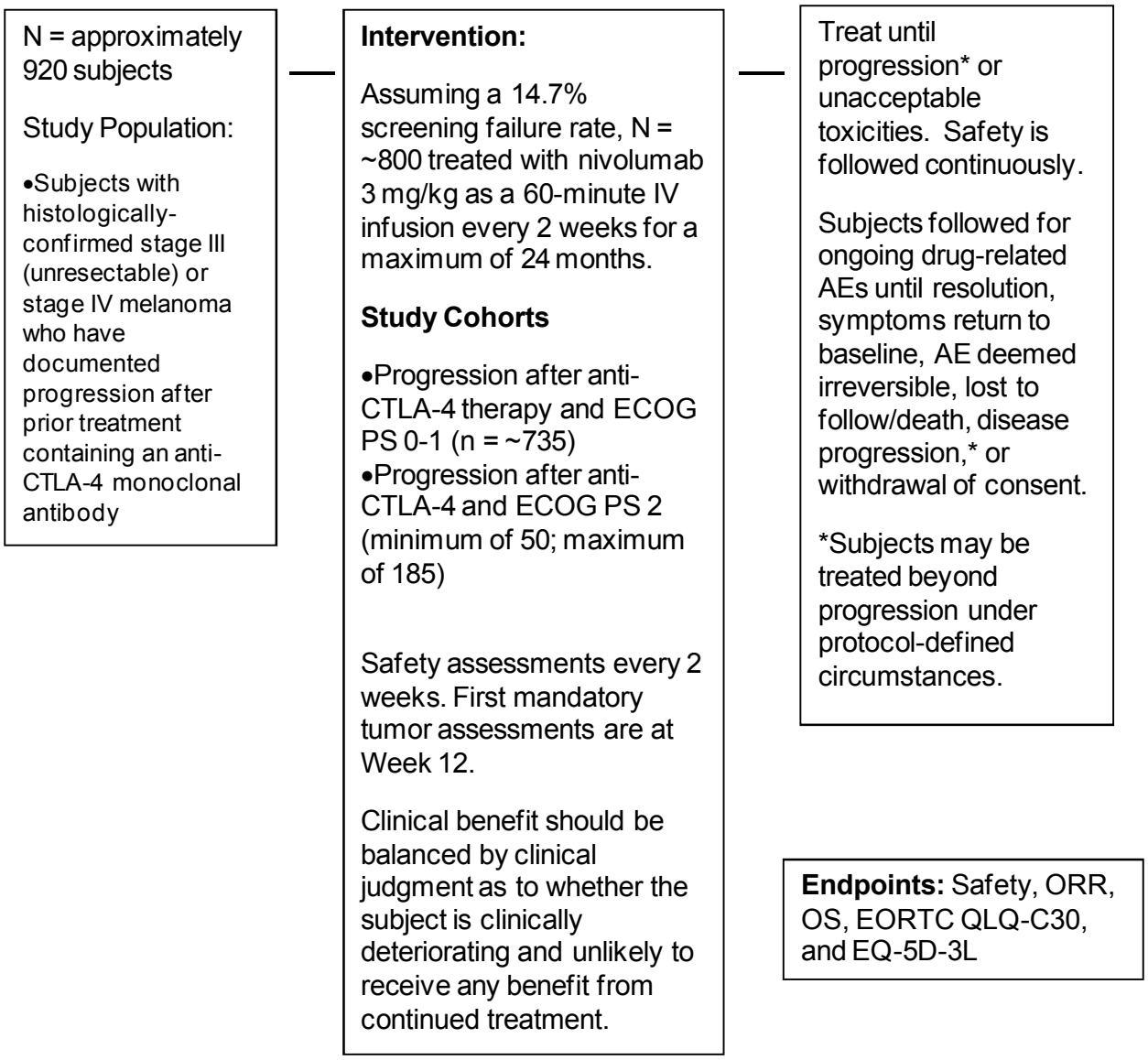
Enrollment of new subjects on the study will stop at the time of marketing authorization approval. In those countries where nivolumab may not be immediately available upon marketing

authorization, enrollment will remain open for a maximum of 1 year after marketing authorization is granted or nivolumab becomes commercially available within the country, whichever occurs sooner.

For those patients enrolled on the study, BMS will continue to provide drug per the timelines defined in the protocol.

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

Figure 3.1-1: Study Design Schematic



3.2 Post Study Access to Therapy

At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study drug up to 12 months after the approval of investigational product by the responsible health authority or until the investigational product becomes

commercially available within the country, whichever occurs sooner. Study drug will be provided via an extension of the study, a rollover study requiring approval by responsible health authorities and ethics committee, or through another mechanism at the discretion of BMS. BMS reserves the right to terminate access to study drug if any of the following occur: a) the marketing application is rejected by the responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a government sponsored or private health program; or d) therapeutic alternatives become available in the local market.

3.3 Study Population

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

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

a) Patients 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 patient care.

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

2. Target Population

a) **Patients with progression after prior treatment containing an anti-CTLA-4 monoclonal antibody (Cohorts 1 and 2):**

i) Patients with histologically confirmed malignant melanoma

ii) Eastern Cooperative Oncology Group (ECOG) PS:

(1) PS 0 to 1 (Cohort 1)

(2) PS 2 (Cohort 2; a minimum of 50 patients and a maximum of 185; clinical risk benefit ratio of Cohort 2 will be monitored by the Scientific Steering Committee)

iii) Previously treated unresectable stage III or stage IV melanoma as per the American Joint Committee on Cancer 2010 Guidelines[36] regardless of BRAF mutation status

iv) Patients must have experienced disease progression or recurrence after prior treatment containing an anti-CTLA-4 monoclonal antibody

v) Prior treatment with chemotherapy, interferon (adjuvant setting), IL-2, BRAF/MEK inhibitors for patients with known BRAF mutations, MEK inhibitors for NRAS mutations, and cKIT inhibitor patients with known cKIT mutations are allowed

vi) Patients with CNS metastases:

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

OR

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

OR

(3) Patients with additional leptomeningeal metastases are eligible if they are treated and neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to enrollment and have a life expectancy of at least 3 months. In addition, patients must be either off corticosteroids or on a stable or decrease dose ≤10 mg daily prednisone (or equivalent)

vii) Prior chemotherapy or immunotherapy (tumor vaccine, cytokine, or growth factor given to control the cancer) must have been completed at least 4 weeks before study drug administration, and all adverse events have either returned to baseline or have been stabilized

viii) Prior palliative radiotherapy must have been completed at least 2 weeks prior to study drug administration

ix) Prior targeted therapy must have been completed at least 2 weeks prior to study drug administration

x) Prior anti-CTLA-4 therapy must have been completed at least 4 weeks before study drug administration

xi) Prior radiotherapy or radiosurgery must have be completed at least 2 weeks prior to the first dose of study drug

xii) Primary uveal (minimum of 30 patients) and mucosal melanoma are allowed

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

(1) WBCs ≥ 2000/μL

(2) Neutrophils ≥1500/μL

(3) Platelets ≥ 100 x 10^3/μL

(4) Hemoglobin ≥ 9.0 g/dL

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

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

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

(6) AST ≤ 3 X ULN

(7) ALT ≤ 3 X ULN

(8) Total bilirubin ≤ 1.5x ULN (except patients with Gilbert Syndrome who must have total bilirubin < 3.0 mg/dL)

xiv) Patients with a known history of Grades 3-4 adverse reactions during anti-CTLA-4 therapy will be allowed to participate if all toxicities have resolved to Grade 1 (NCI CTCAE version 4) or baseline before administration of nivolumab (minimum of 40 patients)

xv) Patients must have evaluable disease by CT or MRI per RECIST 1.1 criteria (radiographic tumor assessment performed within 6 weeks of first dose of study drug) or clinically apparent disease that the investigator can follow for response.

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

b) **As of Amendment 03, this criterion is not applicable.**

i) As of Amendment 03, this criterion is not applicable.

ii) As of Amendment 03, this criterion is not applicable.

(1) As of Amendment 03, this criterion is not applicable.

(2) As of Amendment 03, this criterion is not applicable.

iii) As of Amendment 03, this criterion is not applicable.

(1) As of Amendment 03, this criterion is not applicable.

(2) As of Amendment 03, this criterion is not applicable.

(3) As of Amendment 03, this criterion is not applicable.

iv) As of Amendment 03, this criterion is not applicable.

v) As of Amendment 03, this criterion is not applicable.

vi) As of Amendment 03, this criterion is not applicable.

vii) As of Amendment 03, this criterion is not applicable.

viii) As of Amendment 03, this criterion is not applicable.

(1) As of Amendment 03, this criterion is not applicable.

(2) As of Amendment 03, this criterion is not applicable.

(3) As of Amendment 03, this criterion is not applicable.

(4) As of Amendment 03, this criterion is not applicable.

(5) As of Amendment 03, this criterion is not applicable.

(a) As of Amendment 03, this criterion is not applicable.

(b) As of Amendment 03, this criterion is not applicable.

(6) As of Amendment 03, this criterion is not applicable.

(7) As of Amendment 03, this criterion is not applicable.

(8) As of Amendment 03, this criterion is not applicable.

ix) As of Amendment 03, this criterion is not applicable.

x) As of Amendment 03, this criterion is not applicable.

xi) As of Amendment 03, this criterion is not applicable.

3. Age and Reproductive Status

a) Men and women, aged ≥18 years

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 study drug (s) nivolumab plus 5 half-lives of study drug nivolumab (5 times the half-life = 125 days) plus 30 days (duration of ovulatory cycle) for a total of 155 days or 23 weeks post-treatment completion.

e) Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug nivolumab plus 5 half-lives of the study drug (125 days) plus 90 days (duration of sperm turnover) for a total of 31 weeks post-treatment completion.

f) Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, WOCBP subjects 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% per year when used consistently and correctly.

At a minimum, subjects must agree to the use of two methods of contraception, with one method being highly effective and the other method being either highly effective or less effective as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants, and intrauterine devices (IUDs) such as Mirena® by WOCBP subject or male subject's WOCBP partner. Female partners of male subjects participating in the study may use hormone-based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug.
- Nonhormonal IUDs, such as ParaGard®
- Tubal ligation
- Vasectomy
- Complete abstinence

NOTE: 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.

LESS EFFECTIVE METHODS OF CONTRACEPTION

- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge
- Male condom without spermicide
- Progestin only pills by WOCBP subject or male subject's WOCBP partner
- Female condom

NOTE: A male and female condom must not be used together.

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) As of Amendment 02, this criterion is no longer applicable.

b) Patients with untreated, symptomatic CNS metastases are excluded

2. Medical History and Concurrent Diseases

a) As of Amendment 03, this criterion is not applicable.

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

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

d) 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 patient to receive protocol therapy

e) Any treatment in a BMS-sponsored, interventional nivolumab trial or ipilimumab trial

f) Known drug or alcohol abuse

3. Physical and Laboratory Test Findings

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

b) Positive test for HIV

4. Allergies and Adverse Drug Reaction

a) History of severe hypersensitivity reactions to other monoclonal antibodies

b) History of allergy or intolerance (unacceptable adverse event) to study drug components or Polysorbate-80-containing infusions.

c) As of Amendment 02, this criterion is no longer 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

c) Women treated with ORAL hormone replacement therapy (HRT) are to be excluded unless the oral replacement therapy was stopped by investigator's discretion at least 4 weeks prior to screening and was changed to other contraception method.

6. As of Amendment 02, this criterion is no longer applicable

a) As of Amendment 02, this criterion is no longer applicable

b) As of Amendment 02, this criterion is no longer applicable

c) As of Amendment 02, this criterion is no longer applicable

d) As of Amendment 02, this criterion is no longer applicable

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 duration 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.

3.5 Discontinuation of Subjects Following Any Treatment with Study Drug

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

- Subject's request to stop study treatment
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Maximum of 24 months treatment period from first administration of nivolumab
- Disease progression without investigator-assessed clinical benefit (See Section 4.6.5, Treatment Beyond Disease Progression)
- Additional protocol-specified reasons for discontinuation (See Section 4.6.4)

In the case of pregnancy, the investigator must immediately notify the 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 drug 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 patients will be followed up for select AEs beyond 100 days from the last dose of study therapy, 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 in accordance with Table 5.1-3 until death, lost to follow-up, or withdrawal of study consent.

3.6.1 Withdrawal of Consent

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

3.6.2 Lost to Follow-Up

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

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

4 STUDY DRUG

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, and
- 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.

Table 4.1-1: Study Drugs for CA209172

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
Nivolumab Solution for Injection [a]	100 mg (10 mg/mL)	IP	10 or 5 vials per carton/ Open-label	10 mL per vial/ Open-label; Clear to opalescent, colorless to pale yellow liquid, light (few) particulates may be present.	Store at 2°-8°C (36°-46°F). Protect from light and freezing.

[a] Nivolumab is labeled as BMS-936558-01 Solution for Injection

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).

4.5 Method of Assigning Subject Identification

After the subject's eligibility is established and informed consent has been obtained, the subject will be enrolled, and a number will be assigned through an interactive voice response system (IVRS). Specific instructions and procedures for using IVRS will be provided to the investigational site in a separate document/manual.

4.6 Selection and Timing of Dose for Each Subject

Patients will be treated with 3 mg/kg of nivolumab as a 60-minute (± 5 minutes) IV infusion on Day 1 of a treatment cycle every 2 weeks (14 days) for a maximum of 24 months. No premedications are recommended for initiation of dosing. Dosing calculations should be based on the body weight assessed at each visit as per Table 5.1-2. It is not necessary to re-calculate subsequent doses if the patient's weight is within 10% of the weight used to calculate the previous

dose. All doses should be rounded to the nearest milligram per institutional standard. The screening body weight may be used for dosing of Cycle 1. There will be no nivolumab escalations or reductions permitted. Patients may be dosed no less than 12 days from the previous dose.

Patients will be monitored continuously for AEs while on study. Treatment and modifications (eg, dose delay or discontinuation) will be based on specific laboratory and adverse event criteria.

4.6.1 Nivolumab Dose Delay Criteria

Nivolumab administration should be delayed for the following:

- Grade ≥2 non-skin, drug-related adverse events with the following exceptions:
  - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
- Any Grade 3 skin, drug-related AE
- Any Grade 3 drug-related laboratory abnormalities with the following exceptions for lymphopenia, leukopenia, AST, ALT, or total bilirubin
  - Grade 3 lymphopenia or leukopenia does not require dose delay
  - If a patient has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥2 toxicity
  - If a patient has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥3 toxicity
- Any adverse event, laboratory abnormalities, or undercurrent illness which in the judgment of the investigator, warrants delaying the dose of study medication.

4.6.1.1 Management Algorithms for Immuno-Oncology Agents

Immuno-oncology (I-O) agents are associated with adverse events that can differ in severity and duration from adverse events caused by other therapeutic classes. Nivolumab is considered an immuno-oncology agent in this protocol. Early recognition and management of adverse events associated with immuno-oncology agents may mitigate severe toxicity. Management algorithms can be found in the Investigator's Brochure and have been developed to assist investigators in assessing and managing the following groups of adverse events:

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

For patients expected to require 4 weeks of corticosteroids or other immunosuppressants to manage the adverse event, consider recommendations provided in the Investigator's Brochure.

Tumor assessments for all patients should continue as per protocol even if dosing is interrupted.

4.6.2 Nivolumab Modifications

Nivolumab dose reductions and escalations are not permitted.

4.6.3 Criteria to Resume Treatment with Nivolumab

Patients may resume treatment with nivolumab when the drug-related AEs resolve to Grade ≤1 or baseline value with the following exceptions:

- Patients may resume treatment in the presence of Grade 2 fatigue
- Patients who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- Patients with baseline AST/ALT or total bilirubin in the Grade 1 toxicity range who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST or ALT OR total bilirubin.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment
- If treatment is delayed > 6 weeks, the patient may be permanently discontinued from study therapy, except as specified in Section 3.5.

4.6.4 Discontinuation Criteria for Nivolumab

BMS-936558 (nivolumab) treatment should be permanently discontinued for the following reasons:

- 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-treatment 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, hypersensitivity reactions, and infusion reactions:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
      - AST or ALT > 5-10x ULN for > 2 weeks
      - AST or ALT > 10x ULN
      - Total bilirubin > 5x ULN
      - Concurrent AST or ALT > 3x ULN and total bilirubin > 2x ULN

- 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
  - 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
- Any dosing interruption lasting > 6 weeks 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 patient 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 interruptions > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor. Prior to re-initiating treatment in a patient 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.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the patient with continued nivolumab dosing

4.6.5 Treatment Beyond Disease Progression

As described in Section 1.1.2, accumulating evidence indicated a minority of patients treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease.[37]

Patients treated with nivolumab will be permitted to continue treatment beyond initial Investigator-assessed 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)
- Patient 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 patient is clinically deteriorating and unlikely to receive any benefit from continued treatment with nivolumab

If the investigator feels that the nivolumab patient continues to achieve clinical benefit by continued treatment, the patient should remain on the trial and continue to receive monitoring according to the Time and Events Schedule in Table 5.1-2.

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.

The assessment of clinical benefit should take into account whether the patient is clinically deteriorating and unlikely to receive further benefit from continued treatment. All decisions to continue treatment beyond initial progression must be discussed in the study records.

4.6.6 Treatment of Nivolumab Related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as an SAE if criteria are met. Infusion reactions should be graded according to 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 patient until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) 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 patient with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor patient 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 patient 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 patient until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab

administration. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalence) may be used.

Grade 3 or 4 symptoms (severe reaction, Grade 3 prolonged [ie not rapidly responsive to symptomatic medication and/or brief interruption or 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 patient as follows: recommend bronchodilators, epinephrine 0.2 to 1 mg of 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent) as needed. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor patients until recovery from symptoms. In the 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 the patient'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.

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

4.10 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 Procedural Outline (CA209172)

Procedure	Screening Visit[a]	Visit 1	Notes
Eligibility Assessments			
Informed Consent	X		
Inclusion/Exclusion Criteria	X		Assessed prior to first dose
Medical History	X		Documentation of mutation status (BRAF, NRAS, cKIT) if known.
Safety Assessments			
HIV testing (Germany only)	X		To be performed within 28 days of the first dose.
Physical Examination	X	X	Included height, weight, ECOG Performance Status. Focused physical exam performed at screening, if clinically indicated.
ECOG Performance Status	X	X	Cohort : PS 0-1 Cohort 2: PS 2
Vital Signs and Oxygen Saturation	X	X	Temperature, BP, HR, RR, O2 saturation by pulse oxymetry at rest (also monitor amount of supplement oxygen if applicable). Obtain vital signs at screening visit and within 72 hours of first dose.
Serious Adverse Events Assessment	X	X	
Adverse Events Assessment	X	X	
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]	[redacted]
Laboratory Tests	X		Serum chemistry tests performed locally within 14 days prior to first dose (unless otherwise specified): CBC with differential, serum chemistry (BUN or serum urea level, serum creatinine, sodium, calcium, phosphate, chloride, and glucose), AST, ALT, total bilirubin,

Table 5.1-1: Screening Procedural Outline (CA209172)

Procedure	Screening Visit[a]	Visit 1	Notes
			alkaline phosphatase, albumin, LDH, TSH, free T3, freeT4, and lipase. Within 28 days prior to first dose, hepatitis B surface antigen (HBsAg) and hepatitis C antibody (HCV Ab).
Pregnancy Tests	X	X[b]	Performed within 24 hours prior to first dose for WOCBP only (serum or urine as required by the standard of care at the site). See Section 3.3.3 for the definition of Women of Childbearing Potential.
Additional Assessments			
EORTC QLQ-C30		X	Patient to complete
EQ-5D-3L		X	Patient to complete
Efficacy Assessments			
Screening/Baseline Tumor Assessments	**------see notes------**		Chest, abdomen, pelvis, brain, and other known sites of disease within 6 weeks prior to first dose of study therapy. Patients must have evaluable disease by CT or MRI per RECIST 1.1 criteria (radiographic tumor assessment performed within 6 weeks prior to first dose of study) 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; TSH, thyroid stimulating hormone; WOCBP = women of child bearing potential

[a] Within 6 weeks before start of nivolumab

[b] Within 24 hours prior to the start of nivolumab (Day 1). An extension up to 72 hours prior to the start of nivolumab is permissible in situations where results cannot be obtained within the standard 24 hour window

Table 5.1-2: CA209172 On-Treatment Assessments

Procedure	Each Cycle (every 2 weeks) (±2 days)	Every 2 Cycles (every 4 weeks) (±2 days)	Every 3 Cycles (every 6 weeks) (±2 days)	Notes
Safety Assessments				
Physical Measurements (including PS)	X			Collect weight and ECOG PS within 72 hours prior to dosing. Focused physical exams should be performed as clinically indicated.
Vital Signs and Oxygen Saturation	X			Within 72 hours prior to dosing, tests include temperature, BP, HR, RR, O2 saturation by pulse oxymetry at rest (also monitor amount of supplemental oxygen if applicable) prior to dosing and at any time a patient has any new or worsening respiratory symptoms.
Serious Adverse Event Assessments	X			Assessed using NCI CTCAE v 4.0. For patients with known immune-related, Grades 3-4 adverse events during treatment with an anti-CLTA-4 antibody, weekly telephone calls or in-person visits are recommended.
Adverse Event Assessment	X			Assessed using NCI CTCAE V 4.0. For patients with known immune-related, Grades 3-4 adverse events during treatment with an anti-CTLA-4 antibody, weekly telephone calls or in-person visits are recommended.
[redacted]	[redacted]			
Laboratory Tests	X		X (TFTs only)	CBCs with differential,[a] Serum chemistry tests,[b] liver function tests[c] and lipase should be checked every cycle, and the results should be obtained prior to dosing. TFTs[d] should be checked every 3 cycles (every 6 weeks) starting with Cycle 1. May be completed more frequently if required by local standards. Laboratory tests should be completed 72 hours prior to dosing, and the results must be available prior to dosing. See footnote b regarding availability of lipase results prior to dosing.
Pregnancy Test		X		Completed every 2 cycles, starting with Cycle 1. May be completed more frequently if required by local standards

Table 5.1-2: CA209172 On-Treatment Assessments

Procedure	Each Cycle (every 2 weeks) (±2 days)	Every 2 Cycles (every 4 weeks) (±2 days)	Every 3 Cycles (every 6 weeks) (±2 days)	Notes
Efficacy Assessments				
Tumor Scans	---see notes---			Mandatory initial tumor assessment is to be completed at Week 12 (±5 days). If known or new CNS metastases are detected during screening, a brain scan is required at the mandatory tumor assessment at Week 12 (±5 days). Further tumor assessments are recommended to be completed as required by local standards of care or at the investigator's discretion and are recommended every 8 weeks. The assessment of clinical benefit should be balanced by clinical judgment as to whether the patient is clinical deteriorating and unlikely to receive any benefit from continued treatment with nivolumab.
Survival	X			
Outcomes Assessments				
EQ-5D-3L		X		Every 2 cycles (4 weeks) for 4 months starting with Cycle 1, then every 4 cycles (8 weeks) after first administration of nivolumab prior to any study procedures and treatments
EORTC QLQ-C30		X		Every 2 cycles (4 weeks) for 4 months starting with Cycle 1, then every 4 cycles (8 weeks) after first administration of nivolumab prior to any study procedures and treatments
Clinical Drug Supplies				
Administration of Study Drug	X			

BP = blood pressure; CBC = complete blood count; HR = heart rate; LDH = lactate dehydrogenase; LFT = liver function test; NCI CTCAE = National Cancer Institute Common Terminology Criteria for AEs; O2 = oxygen; PS = Performance Status; RR = respiratory rate; TFT, thyroid function test.

[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

[b] Serum chemistry tests include blood urea nitrogen [BUN] or serum urea level, serum creatinine, sodium, calcium, chloride, lipase, and glucose. Amylase should be performed in addition to lipase in cases where lipase results are not available prior to dosing.

[c] Liver function tests include AST, ALT, total bilirubin, alkaline phosphatase, albumin.

[d] Thyroid function testing including TSH (free T3 and free T4 if abnormal results for TSH).

Table 5.1-3: Off-Treatment Follow-Up Assessments:CA209172

Procedure	Every 4 Weeks	FU-X01 (30 days ±7 days)	FU-X02 (70-84 days after FU-X01 ±7 days)	Follow-Up After X01 and X02. Every 3 months. (±7 days)	Notes
Safety Assessments					.
Physical Examinations		X	X		Collect weight and ECOG PS. Focused physical examination may be performed if clinically indicated.
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 patient has any new or worsening respiratory symptoms.
Adverse Events Assessments		X	X		Beyond 100 days from the last dose of study therapy, patients 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]		
Laboratory Tests		X	X		Serum chemistry tests and TFTs should be checked at FU1 and FU2.
Pregnancy Test	X	X	X		Pregnancy testing may be performed at home if an in-office visit is otherwise not required.
Efficacy Assessments					
Tumor Scans		**-------see notes------**			Tumor progression scans are recommended to be completed as required by local standards of care or at the investigator's discretion.

Table 5.1-3: Off-Treatment Follow-Up Assessments:CA209172

Procedure	Every 4 Weeks	FU-X01 (30 days ±7 days)	FU-X02 (70-84 days after FU-X01 ±7 days)	Follow-Up After X01 and X02. Every 3 months. (±7 days)	Notes
Survival Follow-up		X	X	X[a]	
Outcomes Assessments					
EQ-5D-3L		X	X	X[a]	The EQ-5D-3L can be completed by mail, e-mail, or telephone call (using the telephone version) when a clinical visit is not otherwise required. When a clinical visit is required, the questionnaire should be completed at the clinic.

BP = blood pressure; CBC = complete blood count; HR = heart rate; LDH = lactate dehydrogenase; LFT = liver function test; NCI CTCAE = National Cancer Institute Common Terminology Criteria for AEs; O2 = oxygen; PS = Performance Status; RR = respiratory rate; TFT, thyroid function test.

[a] For subjects who have discontinued treatment before the end of the 2-year treatment period. Per Amendment 08, follow up begins when the decision to discontinue a patient from study therapy is made (no further treatment with nivolumab) and continues from first dose of study therapy up to 2 years or until death, withdrawal of study consent, or lost-to-follow-up.

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 patient'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.

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 and the EORTC QLQ-C30 and EQ-5D-3L.

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 patient's medical record and should not be provided to BMS unless specifically requested. NCI CTCAE version 4.0 will be the criteria used to assess severity of AEs.

During the 100 days after the last dose of study treatment, patients will have 2 additional follow-up visits as described in Table 5.1-3.

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 until discontinuation from study therapy:

- Adverse events continuously throughout the study
- Physical examination and physical measurements including weight and ECOG PS
- Complete blood count with differential, including white blood cells, lymphocyte count, absolute neutrophil count, hemoglobin, hematocrit, and platelet count. Results to be obtained prior to dosing on infusion days.
- Serum chemistry tests (blood urea nitrogen or serum urea level, serum creatinine, sodium, calcium, phosphate, chloride, glucose, lipase, and LDH). Results to be obtained prior to dosing on infusion days. Amylase should be performed in addition to lipase in cases where lipase results are not available prior to dosing.
- Liver function tests including AST, ALT, total bilirubin, alkaline phosphatase, and albumin. Results to be obtained prior to dosing on infusion days.

- Thyroid function testing including thyroid stimulating hormone (free T3 and free T4 if abnormal results for TSH)

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 (seated blood pressure and heart rate), physical measurements, and physical examinations should be performed at program visits.

A full physical examination should be performed prior to the start of treatment. A targeted physical examination may be performed by a qualified professional guided by the examiner's observations and/or patient complaints on new or changed conditions, symptoms, or concerns. Targeted physical exam includes assessment of heart, lungs, and abdomen.

5.3.3 Pregnancy Testing

Pregnancy testing must be completed for WOCBP every 4 weeks while receiving the program drugs and during the follow-up period of 100 days, which includes Follow-up Visits 1 and 2. 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 patients 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

Efficacy assessments include initial mandatory tumor assessment at Week 12 (± 5 days). Further tumor assessments to be completed as required by local standards of care or at the investigator's discretion and are recommended every 8 weeks, as discussed in Table 5.1-2.

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 patient 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 should be performed within 6 weeks prior to first dose of study drug. Brain MRI is the preferred imaging method for evaluating CNS metastasis, and an assessment is required during screening. If known or new CNS metastases are detected during screening, a brain scan is required at the mandatory tumor assessment at Week 12 (±5 days). Furthermore, all known or suspected sites of disease should be assessed at screening and at subsequent assessments using the same imaging method and technique. If more than one method is used at screening, then the most accurate method according to RECIST 1.1 should be used when recording data and should again be used for all subsequent assessments. Bone scan, 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 at Week 12 and using investigator-assessed response thereafter.

Per Amendment 08, patients or their caregivers will be contacted following progression every 3 months either by direct contact or via telephone until death, withdrawal of consent, or lost to follow up for up to 2 years from the start of their treatment with nivolumab. Overall survival will be followed continuously while patients are on the study drug and at follow up visits 1 and 2 as well as every 3 months after discontinuation, or progression, for up to 2 years following the start of therapy either by direct contact (office visits) or via telephone contact, until death, withdrawal of study consent, or lost to follow-up. Overall survival is defined as the time between the start of treatment and the date of death due to any cause. See Table 5.1-3 for further clarification.

Per Amendment 08, survival will be followed after progression either by direct contact (office visits) or via telephone contact until death, withdrawal of study consent, or lost to follow-up for 2 years following start of therapy.

5.5 Pharmacokinetic Assessments

Not applicable.

5.6 Biomarker Assessments

Not applicable.

5.7 Outcomes Research Assessments

Quality-of-life data will be measured using the EORTC QLQ-C30 and EQ-5D-3L questionnaires.

The EORTC QLQ C-30 will be collected in order to assess cancer-specific, health-related quality of life. The EORTC QLQ-C30 is one of the most commonly used QoL instruments in oncology studies and has been assessed in previous studies assessing health-related quality of life in patients with melanoma. The EORTC QLQ-C30 is a 30-item instrument comprising six functional scales (physical functioning, cognitive functioning, emotional functioning, social functioning and global quality of life) as well as nine symptom scales (fatigue, pain, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Except for the overall health status and global quality of life items, responses for all items are 4-point categorical scales ranging from 0 (not at all) to 4 (very much). The overall health status and quality of life responses are 7-point Likert scales.

The EQ-5D-3L comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety) and a visual analog rating scale (VAS).

5.8 Other Assessments

Not applicable.

5.9 Results of Central Assessments

Not applicable. All assessments will be on site.

6 ADVERSE EVENTS

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

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

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

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

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

6.1 Serious Adverse Events

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

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

of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

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

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

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

NOTE:

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

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

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 100 days of discontinuation of dosing (within 30 days of last visit for enrollment/screening failures).

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.

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

All occurrences of overdose must be reported as SAEs (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 evaluate the risk/benefit ratio in general and for the separate prospective cohorts following a predefined Safety Management Plan.

8 STATISTICAL CONSIDERATIONS

The study will include patients with histologically confirmed stage III (unresectable) or stage IV melanoma and progression after prior treatment containing an anti-CTLA-4 monoclonal antibody treated with nivolumab (BMS-936558) at a dose of 3 mg/kg every 2 weeks. Patients will be treated with 3 mg/kg of nivolumab IV every 2 weeks for a maximum of 24 months.

Based on the Performance Status of the patients, there are 2 pre-defined cohorts: Cohort 1, enrolling patients with progression after prior treatment containing an anti-CTLA-4 monoclonal antibody and Performance Status 0-1 (n is at least 640, 85% of the minimum of the 735 screened) and Cohort 2, enrolling patients with progression after prior treatment containing an anti-CTLA-4 monoclonal antibody and Performance Status 2 (n is at the most 160, 85% of the maximum of the 185 screened; a minimum of 50 patients will be enrolled).

A patient who meets the screening criteria will be treated for a maximum of 24 months with safety follow-up at 30 [±7] and 70-84 [±7] days from first follow-up visit post-treatment. With an expected screening failure rate of 15%, a maximum total of about 800 patients (640 PS1 and 160 PS2) will be treated.

The number and percentage of patients with high-grade, treatment-related, select adverse events and their characteristics will be reported overall and by subgroups and during and off-treatment. Overall survival is defined as the time between the start of treatment and the date of death due to any cause. A patient who has not died will be censored at last known date alive. OS will be followed up while patients are on the study drug and every 3 months via in-person visits or phone contact after patients discontinue study drug.

8.1 Sample Size Determination

Currently, there is only little reliable data describing the percentage of patients with melanoma progressing after prior therapy containing treatment with an anti-CTLA-4 monoclonal antibody, presenting with Performance Status 2, and eligible for nivolumab treatment. It is estimated that a minimum of 20% of the potential study population will initially present with PS2. Given that 20% of the 920 patients screened is 185 patients, it is expected that the full complement of 160 patients will be enrolled into the PS2 cohorts and treated.

With an approximate 15% screening failure rate, a cohort of 735 enrolled PS1 patients is projected to a yield 640 treated patients. With n = 640 patients, about 3 will experience a rare adverse event with 0.5% true cumulative event rate with a rate estimated within 95% confidence interval (CI) (0.1%-1.4%). Approximately 2 patients with events and a 95% CI of (0%-1.1%) for assumed true event rate of 0.3% are projected.

8.2 Populations for Analyses

- The safety analysis set comprises patients who received at least 1 dose of nivolumab. The analysis of safety, OS, and QoL data will be based on the safety analysis set.
- The response evaluable analysis set comprises patients who received at least 1 dose of nivolumab and have both baseline and at least 1 post-baseline tumor scan.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

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

Select adverse events are defined in Section 4.6.1.1.

8.3.2 Secondary Endpoint(s)

The secondary endpoints include:

- Incidence of all high-grade (Grades 3 and higher), 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 patient who has not died will be censored at last known date alive. OS will be followed continuously while patients are on treatment and every 3 months via in-person or phone contact after patients discontinue the study drug.

- Investigator-assessed ORR. ORR is defined as the number and percentage of patients with a best overall response (BOR) of confirmed CR or PR. ORR as assessed by the investigator will be reported.

[redacted]

8.4 Analyses

The analysis of primary, secondary (excluding ORR), [redacted] will be reported for the full safety analysis set and by cohorts based on ECOG PS. ORR will be reported for the response evaluable analysis set and by PS. OS and ORR will be further presented by initial investigator-assessed objective response under treatment with an anti-CTLA-4 monoclonal antibody.

Additional details regarding statistical analyses performed in the study are provided in the Statistical Analysis Plan (SAP), which will be finalized before data base lock.

8.4.1 Demographics and Baseline Characteristics

The demographic characteristics, medical history, and baseline assessments of patients will be reported as counts and percentages. The number and percentage of patients by cohorts and subgroups based on types of melanoma (with BRAF-mutated melanoma, uveal melanoma, mucosal melanoma), patients with CNS metastases, patients with known autoimmune disease, and patients who experienced immune-related adverse events during treatment with an anti-CLTA-4 antibody will be presented.

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

8.4.2 Safety Analyses

8.4.2.1 Primary Analyses

The evidence for the research hypothesis of this clinical trial that high-grade (CTCAE v4.0 Grade 3 or higher), treatment-related select adverse events occur with a low frequency in patients with advanced (unresectable or metastatic) melanoma will be presented in terms of the number, percentage of patients, and 95% confidence intervals for the percentage with these select adverse events during and off-treatment overall and by cohort.

8.4.2.2 Secondary Analyses

Adverse events from date of enrollment up to last contact with patients will be presented for the full study duration and separately for events that occur on- or post-treatment. In particular, safety data will be summarized and listed for all treated patients using the NCI CTCAE version 4.0. All on-study AEs, drug-related AEs, SAEs, and drug-related SAEs will be tabulated using worst grade per NCI CTCAE v4.0 criteria by system organ class and MedDRA preferred term. On-study laboratory parameters including hematology, chemistry, liver function, thyroid function, and renal function will be summarized using worst grade per NCI CTCAE v4.0 criteria.

In addition to reporting number and percentages of patients with adverse events, incidence density rates may be reported for repeated adverse events that vary by duration of study participation. Reporting of 95% confidence intervals for incidence density rates will be based on the Poisson distribution.

[redacted]

8.4.3 Efficacy Analyses

Overall survival is defined as the time between the start of treatment and the date of death due to any cause. A patient who has not died will be censored at last known date alive.

OS will be summarized using Kaplan-Meier (KM) product-limit method and associated statistics. Median values of OS, if estimable, along with 2-sided 95% CI using the Brookmeyer and Crowley method will be calculated. Overall survival 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 by subgroups will also be reported. In particular, OS post-treatment will be reported by investigator-reported ORR under treatments with anti-CTLA-4 monoclonal antibody.

ORR is defined as the number and percentage of patients with a best overall response (BOR) of confirmed CR or PR. ORR as assessed by the investigator will be reported.

8.4.4 Pharmacokinetic Analyses

Not applicable.

8.4.5 Biomarker Analyses

Not applicable.

8.4.6 Outcomes Research Analyses

The patients' self-report of their quality of life at baseline and change in their QoL in subsequent visits as recorded in the EORTC QLQ-C30 and EQ-5D-3L questionnaires will be summarized at each time point for the full safety analysis set. In addition, EORTC QLQ-C30 mean domain score and mean change from baseline in domain score will be reported. The overall global health score and domain score (functional and symptom score) for each patient will be calculated using the EORTC QLQ-C30 scoring algorithm. A mixed effects random model may be fitted for the mean change from baseline with time as the main factor and patient level characteristics like age, sex, Performance Status, and other patient characteristics as covariates.

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

8.4.7 Other Analyses

Not applicable.

8.5 Interim Analyses

Several interim analyses will be performed ad hoc and as necessary to address queries from the regulatory authorities.

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 Authorities, 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

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

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

- 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 one 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 two forms 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. 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
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	area under the concentration-time curve
BMS	Bristol-Myers Squibb
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CRF	Case Report Form, paper or electronic
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HRT	hormone replacement therapy
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
IRB	Institutional Review Board
IU	International Unit
IV	intravenous
mg	milligram
MTD	maximum tolerated dose
µg	microgram
N	number of subjects or observations

Term	Definition
N/A	not applicable
NIMP	non-investigational medicinal products
PTT	partial thromboplastin time
SAE	serious adverse event
SD	standard deviation
TAO	Trial Access Online, the BMS implementation of an EDC capability
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential