Official Title of Study:

CLINICAL TRIAL OF NIVOLUMAB (BMS-936558) COMBINED WITH IPILIMUMAB FOLLOWED BY NIVOLUMAB MONOTHERAPY AS FIRST-LINE THERAPY OF SUBJECTS WITH HISTOLOGICALLY CONFIRMED STAGE III (UNRESECTABLE) OR STAGE IV MELANOMA

NCT Number: NCT02599402

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STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

CLINICAL TRIAL OF NIVOLUMAB (BMS-936558) COMBINED WITH IPILIMUMAB FOLLOWED BY NIVOLUMAB MONOTHERAPY AS FIRST-LINE THERAPY OF SUBJECTS WITH HISTOLOGICALLY CONFIRMED STAGE III (UNRESECTABLE) OR STAGE IV MELANOMA

PROTOCOL(S) CA209401

VERSION 2.1

DATE: 25FEB2020

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Schedule of Analyses:

The final analysis will be performed following the database lock after all subjects have completed the study.

During the study, the Scientific Steering Committee (SSC) will closely review the safety data to evaluate the risk/benefit ratio in general and for the separate prospective PS2 subgroup and for subjects treated by ipilimumab monotherapy experienced investigators following a predefined Safety Management Plan.

The Safety Management Plan reviews will include but not be limited to the following frequency and will be triggered by treated patients with ECOG PS2.

- Safety review: Safety review for all treated patients will take place when a minimum of 10 patients in ECOG PS2 subgroup have been dosed with at least 6 weeks of combination regimen therapy (nivolumab combined with ipilimumab) on study to assess safety in all subgroups and evaluate further enrollment into PS2 subgroup.
- Safety review: Safety review for all treated patients will take place when a minimum of 10 patients with at least 12 weeks of combination regimen therapy (nivolumab combined with ipilimumab) on study to assess safety in all treated subjects.
- Subsequent safety reviews: According to the results of previous reviews, further monitoring and subsequent assessments and evaluation of safety will be conducted on a 12-week schedule and data will be provided.

If unexpected events occur, ad hoc telephone conferences with the SSC will be set up.

In addition, a risk/benefit review will be performed for all treated subjects. Initial review for the ECOG PS0-1 subgroup is planned for the first 100 subjects who have been in the study for at least 6 months. According to the results of the safety and risk/benefit reviews, further reviews will be conducted on an as needed basis.

2 STUDY DESCRIPTION

2.1 Study Design

This is a single-regimen, open-label, multicenter, non-randomized, phase 3b study. All patients who meet eligibility criteria will receive the same study treatment regimen. The study consists of three phases: Screening, Treatment, & Follow-up.

The Screening Phase begins by establishing the subject's initial eligibility and signing of the informed consent form. The subject is enrolled using the Interactive Voice Response System (IVRS).

The Treatment Phase begins with the vial assignment call to the IVRS. Study dosing schedules & procedures during the treatment Phase are described as two parts. Part I consists of nivolumab dosing at 1 mg/kg in combination with ipilimumab dosing at 3 mg/kg once every 3 weeks for 12 weeks. Part II consists of nivolumab monotherapy at 3 mg/kg or 240 mg flat dose every 2 weeks until progression or up to a maximum of 24 months of combined study treatment including Part I and Part II. Subject may be treated for more than 24 months for a maximum of 50 cycles in case an on-hold period occurs during the treatment phase. Table 2.1-1 and Table 2.1-2 below describe the schedule for each part of the Treatment Phase of the study.

Table 2.1-1: Treatment Phase: Dosing Schedule for Part I

Every 3 Week Dosing One Cycle = 3 weeks			
Cycle 1	Cycle 2	Cycle 3	Cycle 4
1 mg/kg nivolumab / 3 mg/kg ipilimumab	1 mg/kg nivolumab / 3 mg/kg ipilimumab	1 mg/kg nivolumab / 3 mg/kg ipilimumab	1 mg/kg nivolumab / 3 mg/kg ipilimumab

Table 2.1-2: Treatment Phase: Dosing Schedule for Part II

Every 2 Week Dosing One Cycle = 2 weeks			
Cycle 5	Cycle 6	Cycle 7	Cycle 8 to Cycle 50 (last possible Cycle)
3 mg/kg or 240 mg nivolumab	3 mg/kg or 240 mg nivolumab	3 mg/kg or 240 mg nivolumab	3 mg/kg or 240 mg nivolumab

The Follow-up Phase of the study begins after the conclusion of study treatment.

- Subjects who discontinue therapy in Part I are recommended to be followed by direct contact (office visit) every 4 weeks for up to 100 days after the last dose of combination regimen therapy. After completion of the onsite follow-up visits (for up to 100 days), subjects will be followed every 24 weeks ± 2 weeks for survival either by direct visit or via telephone contact. OS will be followed from the start of therapy up to 2 years or until death, withdrawal of study consent, or lost-to-follow-up, whichever comes first.
- For subjects who complete or discontinue therapy in Part II, subjects will have 2 follow–up visits (office visits): one approximately 30 days after the last dose of study drug and one approximately 100 days after the last dose of study drug. After completion of the first 2 follow-up visits, subjects will be followed every 24 weeks ± 2 weeks for survival either by phone contact or direct contact. OS will be followed in accordance to Event Schedule in Protocol from the start of therapy up to 2 years (+ 100 days following the last dose of study treatment), or until death, withdrawal of study consent, or lost-to-follow-up, whichever comes first.
- For subjects who complete therapy in Part II (2 years of treatment), subjects will have 2 follow-up visits (office visits): one approximately 30 days after the last dose of study drug and one approximately 100 days after the last dose of study drug.

2.2 Treatment Assignment

Subjects meeting eligibility criteria will be assigned a subject number via IVRS. No randomization will take place in the study. All subjects will receive the same treatment regimen as described by the study design.

2.3 Blinding and Unblinding

This study is not blinded.

2.4 Protocol Amendments

This SAP incorporates following protocol amendments.

Table 2.4-1: Protocol Amendments

Amendments	Date of Issue	Summary of Major Changes
Revised Protocol 06	31-JUL-2018	• Follow-up Phase shortened from 5 years after first dose to 2 years after first dose (or 2 years of treatment + 100 days of FU) • For patients discontinued in Part I, follow-up visits will be onsite only • Contraception wording changed based on updated Investigator's Brochure for nivolumab • · Changes made to align with nivolumab program standards
Revised Protocol 05	19-Aug-2016	Incorporates Amendment 06
Amendment 06	19-Aug-2016	Incorporates the updated Pulmonary, Renal, and Skin Adverse Event Management Algorithms that were mistakenly not included in the Revised Protocol associated with Amendment 05.
Revised Protocol 04	03-Aug-2016	Incorporated Amendment 05 and Administrative Letter 02
Amendment 05	03-Aug-2016	• To revise the Management Algorithms to align with the new recommendations • To align with the nivolumab program standards, including changes to the duration of contraception use • To address minor inconsistencies in the protocol • To clarify that tumor assessments beyond Week 12 should be made according to the investigator's assessment.
Administrative Letter 02	28-Jun-2016	• Update the address of the Bristol-Myers Squibb Research and Development facility where the Medical Monitor is located • Clarify that the lettered numbering of the Inclusion Criteria was inadvertently re-numbered during the creation of the revised protocol associated with Amendment 04 • Clarify the Dose Delay Criteria for Grade 2 drug-related creatinine, aspartate aminotransferase, alanine aminotransferase, or total bilirubin • Clarify that tumor scans should also be completed for subjects who discontinue during the nivolumab and ipilimumab combination part (Part I) of the trial.
Revised Protocol 03	25-May-2016	Incorporated Amendment 04 and Administrative Letter 01
Amendment 04	25-May-2016	• Changes the nivolumab monotherapy dose in Part II to 240 mg flat dose for those subjects who enroll after the implementation of Amendment 04 • Decreases the infusion times of nivolumab and ipilimumab • Adds the collection and analysis of biomarkers
Administrative Letter 01	22-Mar-2016	• Align chemistry laboratory procedures throughout the screening, treatment, and follow-up phases and to remove the term serum from these procedures.

Table 2.4-1: Protocol Amendments

Amendments	Date of Issue	Summary of Major Changes
		• Align timing of receipt of testing results and dosing between the Time and Events Schedules and Section 5.3, Safety Assessments. • Add footnotes to Table 5.1-2, On Study Assessments Part I: Cycles 1 through 4 (Nivolumab Plus Ipilimumab) and Table 5.1-3, On-Treatment Assessments Part II: Cycles 5 and Beyond (Nivolumab Monotherapy) to clarify that procedures for each time point should also be delayed if the dose is delayed • Clarify that investigators should follow the Management Algorithms in Appendix 1 for all grade adverse events rather than only Grades 3-4 in the Notes sections of Tables 5.1-2, On-Study Assessments Part I: Cycles 1 through 4 (Nivolumab Plus Ipilimumab) and 5.1-3, On-Treatment Assessments Part II: Cycles 5 and Beyond (Nivolumab Monotherapy). • Remove dosing windows Tables 5.1-2, On-Study Assessments Part I: Cycles 1 through 4 (Nivolumab Plus Ipilimumab) and 5.1-3, On-Treatment Assessments Part II: Cycles 5 and Beyond (Nivolumab Monotherapy). • Add windows to Table 5.1-4, Follow Up Assessments for Subjects who Discontinue in Part I • Align the footnotes and Notes section related collection of adverse events in Tables 5.1-4, Follow Up Assessments for Subjects who Discontinue in Part I and 5.1-5, Follow-Up Assessments for Subjects who Discontinue in Part II to each other for consistency. • Remove the "Every 4 Week Column" from Table 5.1-5, Follow-Up Assessments for Subjects who Discontinue in Part II • Provide clarity on the timing of dosing when lipase test results are not available prior to dosing in Section 5.3, Safety Assessments. • Provide clarity on the timing of dosing in relation to receipt of test results as it differs for baseline assessments and on-treatment assessments.
Revised Protocol 02	05-Feb-2016	Incorporated Amendment 02
Amendment 02	05-Feb-2016	Removed Human Immunodeficiency Virus (HIV) or Acquired Immunodeficiency Syndrome Exclusion Criterion
Revised Protocol 01	06-Jan-2016	Incorporated Amendment 01
Amendment 01	06-Jan-2016	• Changes Exclusion Criteria to known history of Human Immunodeficiency Virus (HIV) or Acquired Immunodeficiency Syndrome and removes HIV testing from the screening procedures. • Adds the definition of a Suspected Unexpected Serious Adverse Event • Requires local regulatory approval if applicable prior implementation of deviations or changes to the protocol.
Original Protocol	03-Jun-2015	Not applicable

3 OBJECTIVES

3.1 Primary

The primary objective of this study is to determine the incidence of high-grade (CTCAE v4.0 Grades 3-5), treatment-related, select adverse events of potentially immune-mediated etiology (pulmonary, gastrointestinal, skin, renal, hepatic, endocrine, infusion related, or hypersensitivity) of nivolumab plus ipilimumab combination regimen as first-line therapy for unresectable or metastatic melanoma.

3.2 Secondary

The secondary objectives of this study are:

- To determine the incidence and to characterize the outcome (duration of serious adverse event [SAE] treatment, dose of immune-modulating agents [ie, steroids] used, time to event onset, and event resolution, and worst grade of event) of high-grade (CTCAE v4.0 Grade 3 or higher), select adverse events of potentially immune-mediated etiology in subjects with unresectable or metastatic melanoma treated with nivolumab and ipilimumab combination regimen.
- To estimate OS in all treated subjects
- To assess safety, tolerability, investigator-assessed objective response rate (ORR), progression-free survival (PFS), and OS in all subjects and in certain subsets of subjects (ECOG PS0-1, ECOG PS2, ocular/uveal, cutaneous, and mucosal melanoma, brain metastasis)

[redacted]

4 ENDPOINTS

4.1 Primary Endpoint

The primary endpoint is the incidence of high-grade (CTCAE v4.0 Grade 3-5), treatment-related, select adverse events of potentially immune-mediated etiology (pulmonary, gastrointestinal, skin, renal, hepatic, endocrine, infusion related or hypersensitivity). Select adverse events of potentially immune-mediated etiology are identified using a custom MedDRA query that is fully defined/updated by BMS and maintained as a separate file (Table A-2). The most recent version will be used for the analysis.

4.2 Secondary Endpoints

The secondary endpoints include those endpoints further relating to the safety and tolerability of the treatment regimen. Also included are response rates, progression, and survival times as described in this Section.

4.2.1 Adverse Events

The incidence of all AEs, treatment-related AEs, serious AEs, and deaths are among the secondary endpoints. In addition, the incidence of all high-grade (Grades 3-5), select adverse events (such as pulmonary, gastrointestinal, skin, renal, hepatic, endocrine, and infusion-related or hypersensitivity) of potentially immune-mediated etiology will be analyzed along with the median time to onset and median time to resolution of select adverse events. Resolution of an AE is a subject experiencing complete resolution or improvement to the baseline grade for the AE.

4.2.2 Laboratory Tests

The rate of subjects experiencing laboratory test abnormalities and the change in results over the course of the study are among the secondary endpoints for the types of tests below.

- Complete blood counts with differentials
- Serum chemistry tests
- Liver function tests
- Thyroid function testing

4.2.3 Overall Survival

OS will be until death, withdrawal of study consent, or lost to follow-up for up to 2 years from the first dose of study treatment. OS is defined as the time between the start of treatment and the date of death due to any cause. A subject who has not died will be censored at last known date alive. OS = (date of death/last know date alive - first dose date)/30.4375 (months).

4.2.4 Progression-Free Survival

Investigator-assessed PFS will be analyzed as a secondary endpoint. A progression event is defined as radiological evidence of progression, significant clinical symptomatic progression, or the need to introduce a non-study drug therapy. Subjects who do not experience those events will be censored based on the scheme in Table 4.2.4-1.

Table 4.2.4-1: Censoring Scheme Used in the Analysis of PFS

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments	First dose	Censored
No on study tumor assessments and no death	First dose	Censored
Progression documented between scheduled visits (per RECIST 1.1 criteria or clinical)	Date of the first documented tumor progression	Progressed
No progression, no death	Date of last tumor assessment with no documented progression	Censored
New anticancer treatment started without a prior reported progression	Date of initiation of the subsequent anti-cancer therapy	Progressed
Death without progression and without subsequent anti-cancer therapy	Date of death	Progressed

PFS = (date of event/censoring - first dose date) / 30.4375 (months).

4.2.5 Objective Response Rate

Overall Response will be assessed by the investigator at clinic visits with scheduled Tumor Assessments and will be assessed according to RECIST 1.1 criteria. These criteria allow for a standard overall assessment to be made based on the status of Target Lesions, Non-Target Lesions, and New Lesions. The overall response is assessed on a nominal categorical scale as one of five responses:

1) Complete Response (CR)
2) Partial Response (PR)
3) Stable Disease (SD)
4) Progressive Disease (PD)
5) Not Evaluable (NE)

The ORR is defined as the number of subjects with a best overall response (BOR) of a complete response (CR) or partial response (PR) divided by the number of all treated subjects. BOR is defined as the best response designation, recorded between the date of first dose and the date of the initial objectively documented tumor progression by the investigator or the date of subsequent therapy, whichever occurs first. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR determination.

The Duration of Objective Response (DOR) is a related secondary endpoint in the study. For subjects achieving an overall response of CR or PR, DOR is calculated as the length of time from the initial PR/CR until the first overall response of PD or death due to any cause, whichever

occurs first. Subjects achieving PR/CR who never progress nor die will be censored on the date of their last tumor assessment.

Time to Objective Response (TTR) is defined as the time from the start of treatment to the date of the first documented response (CR or PR). TTR will be evaluated in all treated subjects and for responders (i.e. subjects with a BOR of CR or PR).

[redacted]

[redacted]

5 SAMPLE SIZE AND POWER

Of 768 subjects who will be screened to receive first-line therapy for advanced disease with histologically confirmed stage III (unresectable) or stage IV melanoma, approximately 615 subjects will be treated with nivolumab and ipilimumab regimen. This sample size is based on the primary objective of the study: determining the incidence of high-grade (CTCAE v4.0 Grades 3-5), treatment-related, select adverse events of potentially immune-mediated etiology in subjects receiving first-line therapy for advanced disease. The sample size will allow for estimating an incidence of about 50% with a 95% CI of (46.06%, 54.11%) under 308 subjects with events among 615 treated subjects.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

While the study is described in Section 2.1 as consisting of three phases including Screening, Treatment, and Follow-up, for the description of the planned statistical analyses, there are two pertinent study periods that will be defined: the Baseline period and the Post-baseline period. These are described in detail in Section 6.1 of the CA209 Core Safety SAP version 5.

6.2 Treatment Regimens

This study is comprised of only a single treatment regimen as described in Section 2.1. Treatment consists of ipilimumab / nivolumab combination treatment once every 3 weeks for 12 weeks (4 cycles total), followed by nivolumab monotherapy every 2 weeks for up to 24 months from first combination dose (Part 1 and Part II). Subject may be treated for more than 24 months for a maximum of 50 cycles in case an on-hold period occurs during the treatment phase.

6.3 Populations for Analyses

The following analysis populations are defined for this study:

- Enrolled subjects: All subjects who signed the informed consent form and obtained a subject number.
- Treated subjects: All subjects who received any study treatment. This is the primary population for safety and efficacy analyses.

- Response evaluable subjects: All treated subjects who have baseline and at least one on-study evaluable tumor measurement.

[redacted]

6.4 Subgroups for Analyses

The study will include several analyses performed according to subgroups of these populations. These subgroups are summarized below. Except for subject enrollment, healthcare resource utilization, outcome research, and PD-L1 expression, all analyses will be performed for all treated subjects and for each subgroup defined in this section.

- ECOG PS subgroups: Subjects will be classified into subgroups based on their baseline ECOG PS grade (0-1 vs 2).
- Brain Metastasis subgroup: Subjects will be grouped into brain metastasis at baseline.
- Disease Subtype subgroup: Subjects will be classified into subgroups based on their disease subtype at baseline (Ocular/Uveal, Mucosal, Cutaneous, Acral, and Other).

In addition, OS will be analyzed based on the following subgroups:

- Best Overall Response subgroups: Subjects will be classified into two subgroups based on their BOR (BOR = CR, PR, SD vs. BOR = PD, NE).

7 STATISTICAL ANALYSES

SAS® version 9.4 or higher will be used for statistical analyses, tabulations and graphical presentations.

7.1 General Methods

The analysis of primary, secondary, and exploratory endpoints will be reported for all treated subjects and/or by subgroups defined in Section 6.4, unless otherwise stated in this SAP.

The CA209 Core Safety DPP refers to several analyses that are to be performed on subjects with extended follow-up. For these summaries, adverse events occurring from the time of the first dose of study therapy through 100 days after the last dose of study therapy will be summarized. Further general methods information for the safety analyses, including general methods for adverse events and laboratory tests can be found in Section 7.1 of the CA209 Core Safety SAP version 5.

7.2 Study Conduct

7.2.1 Accrual

The accrual pattern will be summarized per country, investigational site, and per month for all treated subjects. Enrollment date, first dosing date, country, investigational site will be presented in a by subject listing of accrual.

7.2.2 Relevant Protocol Deviations

The relevant protocol deviations will be summarized for all treated subjects. The following programmable deviations from inclusion and exclusion criteria will be considered as relevant protocol deviations. Non-programmable relevant eligibility and on-treatment protocol deviations, as well as significant (both programmable and non-programmable) eligibility and on-treatment protocol deviations will be reported through CTMS listings.

Eligibility at entrance:

- Subjects without histologically documented unresectable Stage III or Stage IV melanoma, as per AJCC staging system
- Subjects without measurable disease by CT or MRI per RECIST 1.1 criteria at baseline (per Investigator)
- Subject with baseline ECOG performance status > 2
- Women of childbearing potential (WOCBP) had a positive serum or urine pregnancy test at baseline

On-Study:

- Subjects receiving anti-cancer therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents for treatment of cancer) while on study therapy

A by-subject listing of relevant protocol deviations will also be produced.

7.3 Study Population

7.3.1 Subject Disposition

Subject disposition will be listed for all enrolled subjects. For subjects who are treated, the subject's gender, age, race, consent date, vial assignment date (if available), first and last dosing date, off-study date, and reason for going off-study will be listed. For subjects who enroll, but are not treated, the subject's gender, age, race, consent date, and reason for not entering the treatment phase will be listed.

Summary tables reflecting the number of subjects who are enrolled, who are treated, reasons for not entering the treatment phase, and who completed the study will be presented as overall.

The number of subjects who do not complete the study, both overall and according to reasons for discontinuation from the study, will be summarized according to the general methods.

7.3.2 Demographic and Baseline Characteristics

The following baseline characteristics will be summarized for all treated subjects, according to the general methods. All baseline presentations will identify subjects with missing measurements. Listings will also be provided.

- Age (descriptive statistics)

- Age category I (< 65, ≥ 65)
- Age category II (< 65, ≥ 65- < 75, ≥ 75)
- Gender (Male, Female)
- Race (White, Black or African American, American Indian or Alaska Native, Native Hawaiian or Pacific Islander, Asian, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported)
- BRAF mutation status (Wild Type, Mutant, Not Reported)
- Region (EU, Australia)
- Weight (descriptive statistics)
- Height (descriptive statistics)
- Baseline ECOG Performance Status (0, 1, 2)
- Smoking status (Never Smoked, Current/Former, Unknown)
- CNS metastases (Yes, No, Not Reported)
- Treatment status of CNS metastases (Treated, Untreated)
- Subtype of melanoma
- Melanoma stage at study entry (III, IV, Unknown)
- M stage at study entry (M0, M1A, M1B, M1C with Brain Metastases, M1C without Brain Metastases, Unknown)
- Baseline LDH (≤ ULN, > ULN)
- Baseline LDH (≤ 2*ULN, > 2*ULN)
- Time from Initial Disease Diagnosis to Vial Assignment date (if available; otherwise, use first dose date) (< 1 year,1 - < 2 years, 2 - < 3 years, 3 - < 4 years, 4 - < 5 years, ≥ 5 years)
- All lesions (Investigator Tumor Assessments at Baseline): sites of disease, number of disease sites per subject.
- Target lesions (Investigator Tumor Assessments at Baseline): Presence of target lesions, site of target lesion, sum of longest diameter of target lesion.

7.3.3 Medical History

General medical history will be listed by subject.

7.3.4 Prior Cancer Therapy

The following will be summarized by treatment group for all treated subjects, according to the general methods.

- Prior neo-adjuvant therapy (yes/no)
- Prior adjuvant therapy (yes/no)
- Time from completion of prior adjuvant therapy to enrollment (subjects who received prior adjuvant therapy), (< 6 months and > = 6 months)
- Prior surgery related to cancer (yes/no)
- Prior radiotherapy (yes/no)

Agents and medication will be reported using the generic name. A listing by subject will also be provided.

7.3.5 Baseline Examinations

Subjects with abnormal baseline physical exam results will be tabulated by examination criteria (e.g., neck, cardiovascular, lungs, etc.) and for all treated subjects, according to the general methods.

7.4 Extent of Exposure

7.4.1 Administration of Study Therapy

The following parameters will be summarized (descriptive statistics) for all treated subjects, according to the general methods:

- Number of combined doses received (nivolumab + ipilimumab). A subject will be considered to have received combined doses of ipilimumab and nivolumab, if both infusions are administered on the same date.
- Number of doses received (nivolumab by treatment period, ipilimumab)
- Cumulative dose (nivolumab by treatment period, ipilimumab) in mg/kg
- Relative dose intensity (%) using the following categories: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%. (nivolumab by treatment period, ipilimumab)
- Treatment duration (nivolumab by treatment period, ipilimumab) in weeks.

Table 7.4.1-1: Study Therapy Parameter Definitions

	Nivolumab in period 1	Nivolumab in period 2	Ipilimumab in period 1
Dosing Schedule per Protocol	1 mg/kg every 3 weeks for 4 doses	3 mg/kg or 240 mg flat dose every 2 weeks	3 mg/kg every 3 weeks for 4 doses
Actual Dose (mg)	Actual Dose (mg) is defined as the total dose delivered (mg)	Actual Dose (mg) is defined as the total dose delivered (mg)	Actual Dose (mg) is defined as the total dose delivered (mg)
Actual Dose Level (mg/kg)	Actual Dose Level (mg/kg) is defined as the total dose delivered (mg) /most recent weight (kg)	Actual Dose Level (mg/kg) is defined as the total dose delivered (mg) /most recent weight (kg)	Actual Dose Level (mg/kg) is defined as the total dose delivered (mg) /most recent weight (kg)
Cumulative Dose (mg/Kg)	Cumulative Dose (mg/kg) is the sum of the actual dose levels administered to a subject.		Cumulative Dose (mg/kg) is the sum of the actual dose levels administered to a subject.
Relative Dose Intensity (%)	Cumulative dose(mg/kg)/ [1 x (Last dose date – Start dose date + 21)/21] x 100		Cumulative dose(mg/kg) /[3 x (Last dose date - Start dose date + 21)/21] x 100

Table 7.4.1-1: Study Therapy Parameter Definitions

	Nivolumab in period 1	Nivolumab in period 2	Ipilimumab in period 1
Duration of Treatment	Last dose date - Start dose date +1 in period 1	Last dose date - Start dose date +1 in period 2	Last dose date - Start dose date +1 in period 1

*. For post-progression exposure, only doses administrated after progression will be included to derive these parameters.

Duration of treatment will also be presented using a Kaplan-Meier curve whereby the last dose date will be the event date for those subjects who are off study therapy. Median duration of treatment and associated 95% CI will be provided. Subjects who are still on study therapy will be censored on their last dose date.

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

7.4.2 Modifications of Study Therapy

7.4.2.1 Dose Delays

Either nivolumab or ipilimumab infusion may be delayed. A dose will be considered as actually delayed if the delay is exceeding 3 days (i.e. greater than or equal to 4 days from scheduled dosing date) for both nivolumab and ipilimumab. All study drugs must be delayed until treatment can resume. Reason for dose delay will be retrieved from CRF dosing pages.

The number of dose delays per subject, length of delay, and reason for delay will be summarized for all subjects, according to the general methods.

7.4.2.2 Infusion Interruptions and Rate Changes

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

The following parameters will be summarized for all treated subjects, according to the general methods:

- Number of subjects with at least one dose infusion interruption, the reason for interruption, and the number of infusion interruptions per subject.
- Number of subjects with at least one IV infusion rate reduction and the reason for reduction.

7.4.2.3 Dose Escalations

Dose escalations are not permitted for either nivolumab or ipilimumab.

7.4.2.4 Dose Reductions

Dose reductions are not permitted for either nivolumab or ipilimumab.

7.4.2.5 Dose Omissions

Dose omissions are not permitted for either nivolumab or ipilimumab.

7.4.3 Concomitant Medications

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

Concomitant medications will be listed for all treated subjects. Concomitant medications will also be summarized (subjects with any concomitant medication, subjects by medication class and generic term) for all treated subjects, according to the general methods.

7.5 Efficacy

7.5.1 Secondary Analyses

7.5.2 Survival

Overall Survival (OS) and Progression-Free Survival (PFS) will each be summarized using the Kaplan-Meier method. Median values of OS and PFS, along with two-sided 95% confidence intervals using the Brookmeyer and Crowley method will be calculated and presented. Corresponding Kaplan-Meier curves will be produced for OS and PFS based on all treated subjects and subgroups defined in Section 6.4.

7.5.3 Objective Response Rate

The investigator-assessed Objective Response Rate (ORR) will be summarized by binomial response rates and their corresponding two-sided 95% exact confidence intervals using the Clopper-Pearson method. BOR will be tabulated. ORR and BOR will be analyzed for all treated subject as well as subgroups defined in Section 6.4.

7.5.4 Duration of Objective Response

The DOR will be summarized using the Kaplan-Meier method for subjects who achieve a PR or CR. Median values of DOR, along with two-sided 95% confidence intervals using the Brookmeyer and Crowley method, will also be calculated. This analysis will be performed for subjects achieving PR/CR among all treated subjects.

[redacted]

7.6 Safety

7.6.1 Primary Analyses

7.6.1.1 High Grade Treatment-Related Select Adverse Events of Potentially Immune-Mediated Etiology

The number and percentage of subjects who report high-grade (Grade 3-5), treatment-related, select adverse events of potentially immune-mediated etiology (pulmonary, gastrointestinal, skin, renal, hepatic, endocrine, infusion related or hypersensitivity) will be summarized for all treated subjects overall and subgroups. High grade (Grade 3-5) treatment-related select adverse events will be tabulated using worst grade per CTCAE v4.0 criteria by system organ class and Medical Dictionary for Regulatory Affairs (MedDRA) preferred term.

7.6.2 Secondary Analyses

7.6.2.1 High Grade Treatment-Related Select Adverse Events of Potentially Immune-Mediated Etiology in Relevant Subgroups

The number and percentage of subjects who report high grade (Grade 3-5), treatment-related, select adverse events of potentially immune-mediated etiology will be summarized overall and for each subgroup defined in Section 6.4. All high-grade (Grade 3-5), treatment-related, select adverse events will also be tabulated according to the general methods.

7.6.2.2 Select Adverse Events of Potentially Immune-Mediated Etiology

Select adverse events of potentially immune-mediated etiology will be summarized according to their incidence, as well as their time to onset and resolution as described in Section 7.6.6 of the CA209 Core Safety SAP version 5. High grade (Grade 3-5) select adverse events of potentially immune-mediated etiology will also be summarized overall and for each subgroup of interest.

7.6.2.3 Immune-Modulating Medications

Immune-modulating medications received by subjects for the treatment of adverse events will be summarized according to Section 7.6.7 of the CA209 Core Safety SAP version 5 according to the general methods. Immune-modulating medications are defined by a series of search terms according to ATC codes, generic codes, and generic names of medications from the BMS medication coding dictionary that is defined and maintained by BMS in a separate file.

7.6.3 Other Safety Analyses

Other safety analyses will be conducted as below as specified in the CA209 Core Safety SAP version 5.

1) Deaths
2) Serious Adverse Events
3) Adverse Events Leading to Discontinuation of Study Therapy
4) Adverse Events Leading to Dose Modification
5) Adverse Events
6) Multiple Adverse Events

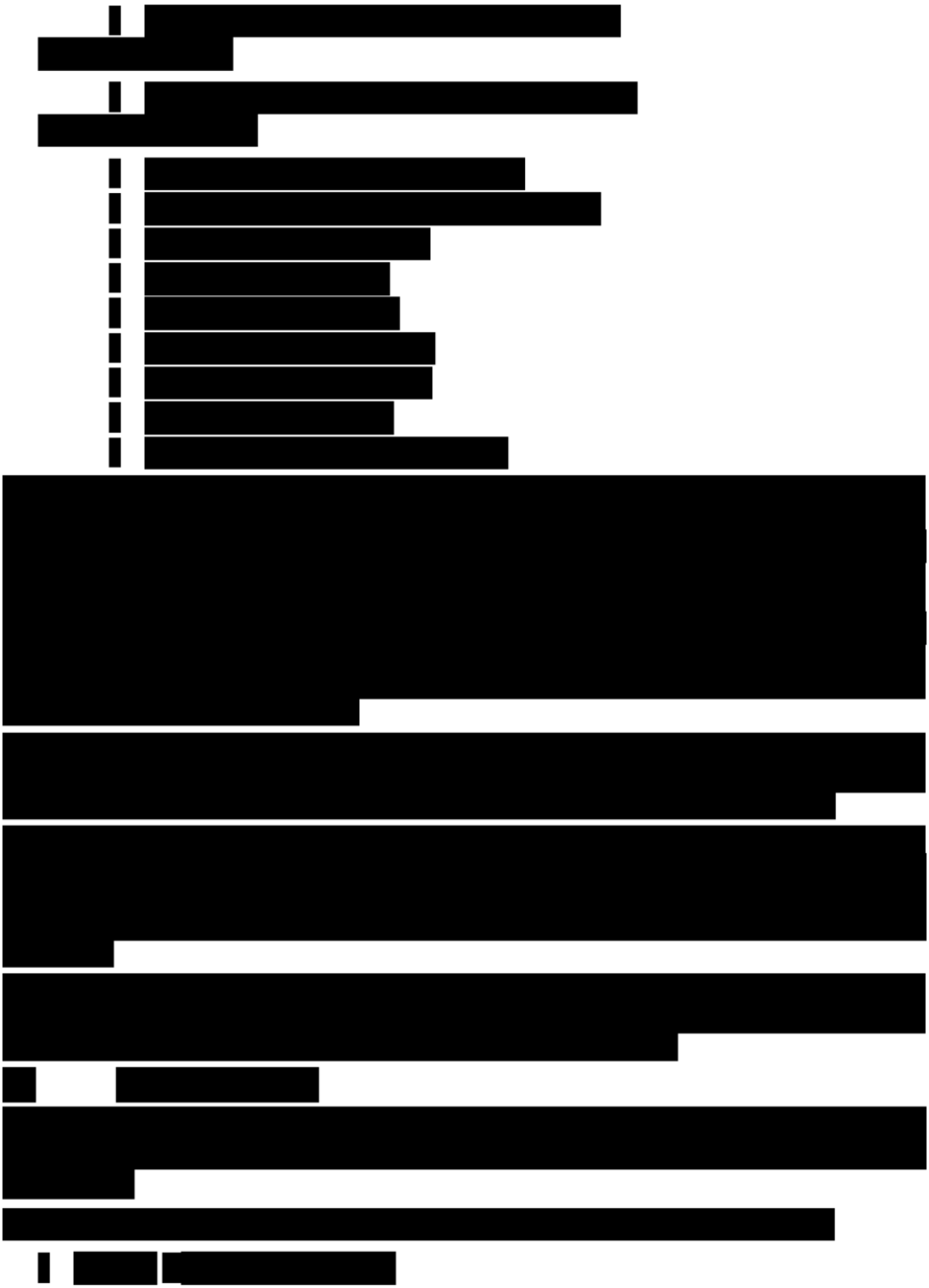
7) Laboratory Parameters
8) Vital Signs and Pulse Oximetry
9) Pregnancy
10) Adverse Events by Demographic Subgroups

7.6.4 Adverse Events by Standardized MedDRA Query (SMQ)

Adverse events will be searched against SMQ and mapped to SMQ term and scope (broad, narrow), only anaphylactic reaction (SMQ) events will be analyzed in this study. AEs and drug-related AEs that started within 48 hours of infusion will be summarized by SMQ/preferred term and by SMQ scope (broad, narrow), respectively. Additional tables will be created as follows for anaphylactic reaction (SMQ) events:

- Total number and exposure adjusted events by SOC/preferred term and SMQ scope (broad or narrow) within 48 hours of infusion,
- Total number and exposure adjusted drug-related events by SOC/preferred term and SMQ scope (broad or narrow) within 48 hours of infusion.

[redacted]



[redacted]

8 CONVENTIONS

Conventions are described in Section 8 of the CA209 Core Safety SAP version 5.

9 CONTENT OF REPORTS

9.1 Clinical Study Report

Statistical components for the clinical study report will be based on the content of this statistical analysis plan (SAP). Details of the tables, listings, and figures to be prepared for the final CSR will be included in a study-specific Data Presentation Plan (DPP).

9.2 Other Reports and Reviews

The Scientific Steering Committee will closely review the safety data throughout the study to evaluate the overall risk/benefit profile as well as within the ECOG PS2 subgroup.

9.2.1 Safety Reviews

Safety reviews will begin when the following milestones have been met on the study:

- Ten patients in the ECOG PS2 subgroup have been dosed with at least 6 weeks of combination regimen therapy.
- Ten patients overall have been dosed with at least 12 weeks of combination therapy.

Once the initial safety review is concluded, the Scientific Steering Committee will conduct further reviews according to the previous results every 12 weeks. Safety reviews will include the following summaries:

- Subject disposition
- Demographics and other baseline characteristics
- Physical measurements and baseline disease characteristics

- AEs with focus on:
  a) All or drug-related AEs
  b) Immune-mediated, select AEs: incidence of all or drug-related event, time to onset and time to resolution
  c) AEs leading to discontinuation of treatment
  d) SAEs
- Subject death
- ECOG performance status over time
- Concomitant medication for drug-related selected AEs
- Time on study
- Doses and duration of study therapy

[redacted]

10 DOCUMENT HISTORY

Version Number	[redacted]	Date of Changes	Description
1.0	[redacted]	25Jan2018	Final version for approval
2.0	[redacted]	28Jan2019	Update per revised protocol v6.0

Version Number [redacted]	Date of Changes	Description
2.1 [redacted]	27Jan2020	Deleted the subgroup analysis related to Weight base vs flat dose, and Non-Brain Metastatic column.
2.1 [redacted]	31Jan2020	The subgroups of weight-based vs. flat dose, and non-brain metastatic are removed from analyses, as they are not specified in the protocol.
2.1 [redacted]	23Feb2020	1)Corrected dates of change above.

APPENDIX 1 SELECT ADVERSE EVENTS DEFINITION AND CONVENTIONS

The select Adverse Events (select AEs) consist of a list of preferred terms grouped by specific category (e.g. pulmonary events, gastrointestinal events categories) and by subcategory (e.g. thyroid disorders, diabetes, pituitary, adrenal disorders subcategories). These categories and subcategories are defined by the Sponsor and the list that is most current at the time of analysis will be used. Also, changes may be made to this list with each new version of MedDRA.

For information, the select adverse events defined at the time of finalization of the first version of the document are listed in Table A-2 using MedDRA version 20.1. The final list used for the clinical study report will be included in an Appendix of the CSR.

Time-to onset definition

Time-to onset of select AE (any grade) for a specific category (i.e. pulmonary events, gastrointestinal events, ...) is defined as the time between the day of the first dose of study treatment and the onset date of the earliest select AE (of any grade) in this category.

If the subject did not experience a select AE (of any grade) in the category, time-to onset will be censored at the maximum follow-up time of all subjects in their respective treatment group (i.e for subjects without an event, follow-up time is defined from first dosing date up to last dosing date +30 days (or 100 days depending on the analysis) if subjects are off treatment and followed for at least 30 days (or 100 days depending on the analysis) , otherwise it is defined up to the last known alive date). The resulting Kaplan-Meier plot will represent the cumulative rate of the select AE (any grade) in the category over time.

Time-to onset of select AE (grade 3-5) for a specific category is defined similarly but restricted to grade 3-5 select AEs.

Time-to onset of drug-related (grade 3-5 or any grade) select AE for a specific category is defined similarly but restricted to drug-related select AEs.

Time-to onset for a specific subcategory is defined similarly but restricted to event of this subcategory.

Time-to resolution definition

In order to derive the time-to resolution, overlapping or contiguous select AEs within a specific category (defined in Table A-2) will be collapsed into what will be termed “clustered” select AEs. For example, if a subject (without pre-treatment AE) experienced an AE from 1st to 5th January, another AE (with different PT but within same category) from 6th to 11th January and same AE from 10th to 12th January, these will be collapsed into one clustered select AE from 1st to 12th January. Table A-1 is summarizing key derivation steps for each type of clustered select AEs.

Time-to resolution of select AE (any grade) for a specific category is defined as the longest time from onset to complete resolution or improvement to the grade at baseline among all clustered select AEs in this category experienced by the subject. Events which worsened into grade 5

events (death) or have a resolution date equal to the date of death are considered unresolved. If a clustered select AE is considered as unresolved, the resolution date will be censored to the last known date alive. Improvement to the grade at baseline implies that all different AE events in the clustered select adverse event should at least have improved to the corresponding (i.e. with same preferred term) baseline grade. This measure is defined only for subjects who experienced at least one select AE in the specific category.

The time-to resolution of select AE (grade 3-5) for a specific category is defined similarly with an onset date corresponding to a grade 3-5 select AE.

Time-to resolution of drug-related select AE (any grade or grade 3-5) is defined similarly but restricted to drug-related select AE.

The time-to resolution of select AE (any grade or grade 3-5, drug-related or all) where immune modulating medication was initiated is defined similarly with the additional condition that the subject started an immune modulating medication during the longest select AE resolution period.

Time-to resolution for a specific subcategory is defined similarly but restricted to event of this subcategory.

Table A-1: Derivation of clustered select AE

Type of clustered select AE	Derivation
Any grade	Collapse any on-treatment select AE from the same category
Drug-related of any grade	Collapse any on-treatment drug-related select AE from the same category
Grade 3-5	Collapse any on-treatment select AE from the same category. Resolution will be based on the onset date of the earliest grade 3-5 records (if no grade 3-5 record, clustered select AE is excluded)
Drug-related of Grade 3-5	Collapse any on-treatment drug-related select AE from the same category Resolution will be based on the onset date of the earliest grade 3-5 record (if no Grade 3-5 record, clustered select AE is excluded)

The algorithm for collapsing select adverse event records is using the following conventions:

For each subject and specified category, the corresponding adverse event records will be collapsed when:

1) Multiple adverse event records have the same onset date.
2) The onset date of an event record is either the same day or 1 day later than the resolution date of a preceding event record (contiguous events).
3) The onset date of an event record is after the onset date and prior to or on the resolution date of a preceding event record (overlapping events).

Table A-2: Select Adverse Events

Category	Subcategory	Preferred Terms
ENDOCRINE ADVERSE EVENT	ADRENAL DISORDER	ADRENAL INSUFFICIENCY
		ADRENAL SUPPRESSION
		ADRENOCORTICAL INSUFFICIENCY ACUTE
		BLOOD CORTICOTROPHIN DECREASED
		BLOOD CORTICOTROPHIN INCREASED
		HYPOTHALAMIC PITUITARY ADRENAL AXIS SUPPRESSION
		PRIMARY ADRENAL INSUFFICIENCY
		SECONDARY ADRENOCORTICAL INSUFFICIENCY
	DIABETES	DIABETES MELLITUS
		DIABETIC KETOACIDOSIS
		FULMINANT TYPE 1 DIABETES MELLITUS
		LATENT AUTOIMMUNE DIABETES IN ADULTS
		TYPE 1 DIABETES MELLITUS
	PITUITARY DISORDER	HYPOPHYSITIS
		HYPOPITUITARISM
		LYMPHOCYTIC HYPOPHYSITIS
	THYROID DISORDER	ATROPHIC THYROIDITIS
		AUTOIMMUNE HYPOTHYROIDISM
		AUTOIMMUNE THYROIDITIS
		BASEDOW'S DISEASE
		BLOOD THYROID STIMULATING HORMONE DECREASED
		BLOOD THYROID STIMULATING HORMONE INCREASED
		HYPERTHYROIDISM
		HYPOTHYROIDISM
		PRIMARY HYPERTHYROIDISM
		PRIMARY HYPOTHYROIDISM
		SILENT THYROIDITIS
		THYROID FUNCTION TEST ABNORMAL
		THYROID HORMONES DECREASED
		THYROID HORMONES INCREASED
		THYROIDITIS
		THYROIDITIS ACUTE
		THYROXINE DECREASED
		THYROXINE FREE DECREASED
		THYROXINE FREE INCREASED
		THYROXINE INCREASED
		TRI-IODOTHYRONINE UPTAKE INCREASED
GASTROINTESTINAL ADVERSE EVENT		AUTOIMMUNE COLITIS
		COLITIS

Table A-2: Select Adverse Events

Category	Subcategory	Preferred Terms
		COLITIS ULCERATIVE
		DIARRHOEA
		ENTERITIS
		ENTEROCOLITIS
		FREQUENT BOWEL MOVEMENTS
		GASTROINTESTINAL PERFORATION
		LOWER GASTROINTESTINAL PERFORATION
		UPPER GASTROINTESTINAL PERFORATION
HEPATIC ADVERSE EVENT		ACUTE HEPATIC FAILURE
		ACUTE ON CHRONIC LIVER FAILURE
		ALANINE AMINOTRANSFERASE INCREASED
		ASPARTATE AMINOTRANSFERASE INCREASED
		AUTOIMMUNE HEPATITIS
		BILIRUBIN CONJUGATED INCREASED
		BLOOD ALKALINE PHOSPHATASE INCREASED
		BLOOD BILIRUBIN INCREASED
		DRUG-INDUCED LIVER INJURY
		GAMMA-GLUTAMYLTRANSFERASE INCREASED
		HEPATIC ENZYME INCREASED
		HEPATIC FAILURE
		HEPATITIS
		HEPATITIS ACUTE
		HEPATOTOXICITY
		HYPERBILIRUBINAEMIA
		LIVER DISORDER
		LIVER FUNCTION TEST ABNORMAL
		LIVER FUNCTION TEST INCREASED
		LIVER INJURY
		TRANSAMINASES INCREASED
HYPERSENSITIVITY/INFUSION REACTION		ANAPHYLACTIC REACTION
		ANAPHYLACTIC SHOCK
		BRONCHOSPASM
		HYPERSENSITIVITY
		INFUSION RELATED REACTION
PULMONARY ADVERSE EVENT		ACUTE RESPIRATORY DISTRESS SYNDROME
		ACUTE RESPIRATORY FAILURE
		IDIOPATHIC INTERSTITIAL PNEUMONIA
		INTERSTITIAL LUNG DISEASE
		LUNG INFILTRATION

Table A-2: Select Adverse Events

Category	Subcategory	Preferred Terms
		PNEUMONITIS
RENAL ADVERSE EVENT		ACUTE KIDNEY INJURY
		AUTOIMMUNE NEPHRITIS
		BLOOD CREATININE INCREASED
		BLOOD UREA INCREASED
		CREATININE RENAL CLEARANCE DECREASED
		HYPERCREATININAEMIA
		NEPHRITIS
		NEPHRITIS ALLERGIC
		PARANEOPLASTIC GLOMERULONEPHRITIS
		RENAL FAILURE
		RENAL TUBULAR NECROSIS
		TUBULOINTERSTITIAL NEPHRITIS
		URINE OUTPUT DECREASED
SKIN ADVERSE EVENT		AUTOIMMUNE DERMATITIS
		BLISTER
		DERMATITIS
		DERMATITIS ALLERGIC
		DERMATITIS EXFOLIATIVE
		DRUG ERUPTION
		ECZEMA
		ERYTHEMA
		ERYTHEMA MULTIFORME
		EXFOLIATIVE RASH
		FIXED DRUG ERUPTION
		NODULAR RASH
		PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME
		PEMPHIGOID
		PHOTOSENSITIVITY REACTION
		PRURITUS
		PRURITUS ALLERGIC
		PRURITUS GENERALISED
		PSORIASIS
		RASH
		RASH ERYTHEMATOUS
		RASH GENERALISED
		RASH MACULAR
		RASH MACULO-PAPULAR
		RASH MORBILLIFORM

Table A-2: Select Adverse Events

Category	Subcategory	Preferred Terms
		RASH PAPULAR
		RASH PRURITIC
		RASH VESICULAR
		SKIN EXFOLIATION
		SKIN HYPOPIGMENTATION
		SKIN IRRITATION
		STEVENS-JOHNSON SYNDROME
		TOXIC EPIDERMAL NECROLYSIS
		TOXIC SKIN ERUPTION
		URTICARIA
		VITILIGO

Source: MedDRA version 20.1