Official Title of Study:

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

NCT Number: NCT02156804

Document Date (Date in which document was last revised): June 13, 2019

STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

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

PROTOCOL CA209-172

VERSION # 4.0

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Research Hypothesis:

High-grade (CTCAE v4.0 Grade 3 or higher), treatment-related, select adverse events occur with a low frequency in subjects 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.

Schedule of Analyses:

Several interim analysis will be conducted ad-hoc and as necessary to address queries from regulatory authorities.

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 subgroups following a predefined Safety Management Plan.

The final analysis will be conducted only after subjects who have met the screening criteria have been 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.

2 STUDY DESCRIPTION

2.1 Study Design

The study will include subjects with histologically-confirmed stage III (unresectable) or stage IV advanced melanoma who have documented progression after treatment containing an anti-CTLA-4 monoclonal antibody. Subjects will be treated with 3 mg/kg of nivolumab IV every 2 weeks for a maximum of 24 months. Subjects 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.

Subjects will undergo screening evaluations to determine eligibility prior to first dose following signed informed consent. Subject'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 events and physical examination, should be monitored continually, and safety assessments are discussed in Tables 5.1-1 and 5.1-2 of the protocol.

Mandatory initial tumor assessments are to be done at Week 12 (+/-7 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 subject is lost to follow up
- the subject withdraws study consent
- completed 24 months of treatment

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

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

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

Follow up begins when the decision to discontinue a subject from study therapy is made (no further treatment with nivolumab) and continues up to 5 years from first dose of study therapy until death, withdrawal of study consent, or lost-to-follow-up.

The cohorts are described in Table 1.

Table 1: Subject Cohorts

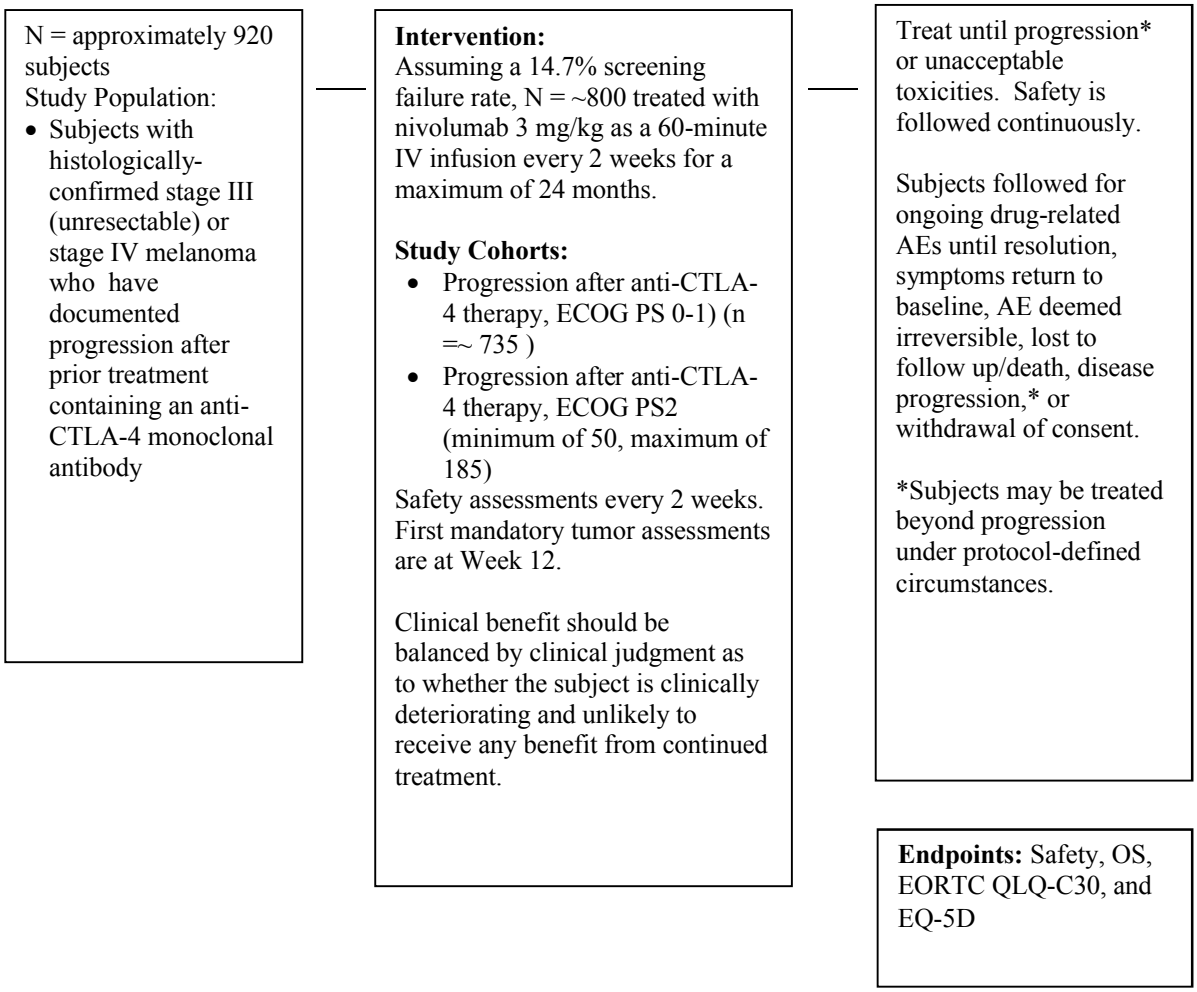
(Cohort Number)	Disease Criteria
Cohort 1: Advanced Melanoma (unresectable stage III or stage IV) (N > 735)	• ECOG Performance Status 0 to 1 • Progressing after prior therapy containing treatment with an anti-CTLA-4 monoclonal antibody
Cohort 2: Advanced Melanoma (unresectable stage III or stage IV)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

Figure 1: Study Design Schematic



2.2 Treatment Assignment

Because this is an open label study with everyone receiving the same treatment, no treatment assignment is needed. Subjects will be enrolled into study cohorts (see Table 1) based on their disease characteristics at screening.

Enrolled subjects will be assigned a unique identification number. The subject number will be assigned through an interactive voice response system (IVRS) once the subject has signed the informed consent form and is registered. Every subject that signs the informed consent form must be assigned a subject number in IVRS. Specific instructions for using IVRS will be provided to that investigational site in a separate document.

2.3 Blinding and Unblinding

Not applicable. This is an open-label study.

2.4 Protocol Amendments

There are currently 6 approved amendments. Table 2 shows the history of protocol amendments including the dates and change history to the protocol.

Table 2: Protocol Amendments

Document	Date	Summary of Changes
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

Table 2: Protocol Amendments

Document	Date	Summary of Changes
Amendment 03	19-Mar-2015	• This Amendment removes the inclusion of the treatment-naïve subjects, 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. • [redacted]. • The options for palliative local therapy have also been expanded to meet the needs of the current subject populations. • The EORTC QLQ-C30 has been eliminated from the subject 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, and [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

Table 2: Protocol Amendments

Document	Date	Summary of Changes
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	Original Protocol

2.5 Scientific Steering Committee

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 subgroups following a predefined Safety Management Plan

3 OBJECTIVES

3.1 Primary

The primary objective of this study is:

- To determine the incidence of high-grade (CTCAE v4.0 Grade 3 or higher), treatment-related, select adverse events in subjects with histologically confirmed stage III (unresectable) or stage IV melanoma and progression after prior treatment containing an anti-CTLA-4 monoclonal antibody treated.

3.2 Secondary

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 subjects with histologically confirmed stage III (unresectable) or stage IV melanoma and progression after prior treatment containing an anti-CTLA-4 antibody;
- To estimate OS in all treated subjects.

[redacted]

4 ENDPOINTS

4.1 Primary Endpoint

The primary endpoint is the incidence for high-grade (CTCAE v4.0 Grade 3 or higher), treatment-related, select adverse events. The select Adverse Events consist of a list of preferred terms grouped by specific category as follows:

- Pulmonary toxicity
- Gastrointestinal toxicity (diarrhea or colitis)
- Endocrinopathies
- Hepatotoxicity (including asymptomatic LFT elevations)
- Renal toxicity
- Skin toxicity
- Hypersensitivity/Infusion site reaction

4.2 Secondary Endpoints

The secondary endpoints include the incidence of all high-grade (Grades 3 and higher) select adverse events, the median time to onset and median time to resolution (Grades 3-4) of select adverse events, the and overall survival (OS) of subjects.

4.2.1 Incidence of all High-grade, Select AEs

The incidence for high-grade (CTCAE v4.0 Grade 3 or higher), select adverse events. The select Adverse Events consist of a list of preferred terms grouped by specific category as follows:

- Pulmonary toxicity
- Gastrointestinal toxicity (diarrhea or colitis)
- Endocrinopathies
- Hepatotoxicity (including asymptomatic LFT elevations)
- Renal toxicity
- Skin toxicity
- Hypersensitivity/Infusion site reaction

4.2.2 *Median Time to Onset and Resolution of Select AEs*

The median time to onset and the median time to resolution will be calculated for the list of select AEs defined in section 4.2.1. The time to onset is defined as the time from treatment start (first dose, first cycle) to AE start for each individual AE. The time to resolution is defined as the time from AE start to AE stop for each individual AE.

4.2.3 *Overall Survival (OS)*

Overall survival (OS) is defined as the time from the date of first dose until the date of death. For those subjects who have not died, OS will be censored on the last date the subject was known to be alive. OS will be followed continuously while subjects are on treatment and every 3 months via in-person or phone contact after subjects discontinue the study drug.

[redacted]

[redacted]

Table 3: Time Windows for Assessments

Nominal Time-Point	Time Window
Week 1 (Baseline)	Prior to first dose on Day 1
Week 5	Day 2 thru Day 55, inclusive
Every 4 weeks up to Week 13	Nominal day (+26 days/-2 days, inclusive)
Week 17	Nominal day 113 (+54 days/-2 days, inclusive)
Every 8 weeks thereafter	Nominal day (+54 days/-2 days, inclusive)
Follow-up 1 (EQ-5D-3L only)	If assessment is post last dose and within 30 days of last dose (+68-82 days/-2 days, inclusive)
Follow-up 2 (EQ-5D-3L only)	If assessment is post 70-84 days of Follow-up 1 (+89 days/-2 days, inclusive)
Every 3 months thereafter (EQ-5D-3L only)	If assessment is after Follow-up 1 and Follow-up 2 (+89 days/-2 days, inclusive)

4.3.3.2 EuroQoL EQ-5D-3L

Subjects' reports of general health status will be assessed using the EuroQoL Group's EQ-5D-3L. EQ-5D-3L essentially has 2 components: the descriptive system and the visual analogue scale (VAS).

The instrument's descriptive system consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels, reflecting "no health problems," "moderate health problems," and "extreme health problems." A dimension for which there are no problems is said to be at level 1, while a dimension for which there are extreme problems is said to be at level 3. Thus, the vectors 11111 and 33333 represent the best health state and the worst health state, respectively, described by the EQ-5D-3L. Altogether, the instrument describes $3^5 = 243$ health states. Empirically derived weights can be applied to an individual's responses to the EQ-5D-3L descriptive system to generate an index measuring the value to society of his or her current health. Such preference-weighting systems have been developed for the UK, US, Spain, Germany, and numerous other populations. For this study, EQ-5D-3L utility index values will be computed using a scoring algorithm based on the United Kingdom Time-Trade-Off (UK TTO) value set[2]

In addition, the EQ-5D-3L includes a VAS, which allows respondents to rate their own current health on a 101-point scale ranging from 0="worst imaginable" health to 100="best imaginable" health state[3].

A change from baseline of 0.08 for the EQ-5D-3L utility index score and of 7 for the EQ-5D-3L VAS are considered minimally important differences for the EQ-5D-3L[4].

All questionnaires completed at baseline and on-study will be assigned to a time-point according to the windowing criteria in Table 3 and included in the analysis. In case a subject has two on-study assessments within the same window, the assessment closest to the time-point will be used.

And, in the case of two assessments at a similar distance to the time-point, the latest one will be chosen. In the event where the subject has no assessment at all in a specific window, the observation will be treated as missing for that time-point.

5 SAMPLE SIZE AND POWER

Currently, there is only little reliable data describing the percentage of subjects 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 approximately 20% of the 920 subjects screened is 185 subjects, it is expected that the full complement of 160 subjects will be enrolled and treated in the PS2 cohort.

With an approximate 15% screening failure rate, a cohort of 735 screened PS1 subjects is projected to yield 640 treated subjects. With n = 640 subjects, 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 subjects with events and a 95% CI of (0%-1.1%) for assumed true event rate of 0.3% are projected.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Period

See Section 6.1 of the Core Safety SAP.

6.2 Treatment Regimens

Subjects 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. It is not necessary to re-calculate subsequent doses if the subject'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. Subjects may be dosed no less than 12 days from the previous dose.

6.3 Populations for Analyses

The following analysis populations are defined for this study:

- **All Enrolled analysis set**: All subjects who signed an informed consent form and were registered into the IVRS.
- **All Treated analysis set**: All enrolled subjects who received at least 1 dose of nivolumab
- **Response evaluable analysis set:** All enrolled subjects who received at least 1 dose of nivolumab and have both baseline and at least 1 post-baseline tumor scans.

6.4 Subpopulations for Analyses

The study will include several analyses performed according to subpopulations (cohorts). These subpopulations are summarized below. Except where otherwise stated, all analyses will be performed for all treated subjects, as overall and for each subpopulation defined in this section.

- Mucosal population: Subjects have their baseline type of melanoma as mucosal.
- Cutaneous population: Subjects have their baseline type of melanoma as cutaneous.
- Ocular/Uveal population: Subjects have their baseline type of melanoma as ocular/uveal.
- Acral: Subjects have their baseline type of melanoma as acral.
- Other subtype of melanoma: Subjects have their baseline type of melanoma as other.
- ECOG PS 2 population: Subjects have their baseline ECOG PS grade of 2.
- CNS metastasis population: Subjects will be classified into this group based on the evidence of brain metastasis at baseline. Subjects with CNS metastasis are those who answered "MIC WITH BRAIN METASTASES" on the "M Status" question of the "Initial/Current Disease Diagnosis" form of the CRF (Yes).
- BRAF Mutation population: Subjects have their baseline BRAF mutation status with Mutant defined as all mutations of V600 (e.g., V600, V600E, V600K, V600D, or V600R) and all remaining (no mutation or non-V600 mutations) defined as Wildtype.
- Autoimmune disease population: Subjects will be classified into this group if they report a history of autoimmune disease at baseline.
- Experience of immune-related AE during treatment with an anti-CTLA-4 antibody: Subjects will be classified into this group based on subject's experience of Grade 3-4 immune-related AE during treatment with an anti-CTLA-4 antibody (Yes).

7 STATISTICAL ANALYSES

7.1 General Methods

In the analysis described below (except where noted), counts and percentages will be reported for discrete variables with inclusion of unknown or missing values as a separate category. The mean, standard deviation, median, range (minimum and maximum), and number of non-missing values will be reported for each continuous measure.

Adverse events and medical history will be coded according to the most recent Medical Dictionary for Regulatory Activities (MedDRA). Previous and [redacted] will be coded using the WHO Drug Dictionary.

The time to event distribution (i.e. overall survival) will be estimated using Kaplan Meier techniques. Median for time to event endpoints along with 95% confidence interval (CI) will be constructed based on 95% CI using the Brookmeyer and Crowley[1] method. 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.

All data summaries, unless otherwise noted, will be presented by subpopulations. A total column will be included in each summary.

- Mucosal
- Cutaneous
- Ocular/Uveal
- Acral
- Other
- ECOG PS2
- CNS Metastasis
- Autoimmune disease
- Grade 3-4 irAEs with anti-CTLA-4

Tables that will be presented by baseline LDH, BRAF mutation and type of autoimmune disorder should have the following presentation order:

- Baseline LDH: ≤ ULN, > ULN, and > 2*ULN
- BRAF status: Mutant, Wildtype, and Not reported, if no BRAF genetic mutation results are available.
- Type of autoimmune disorder: Endocrine, Gastrointestinal, Hepatic, Skin, and Other

Further, general methods information for the safety analysis, including general methods for adverse events and laboratory tests can be found in Section 7.1 of the CA209 Core Safety SAP version 4. Statistical analyses will be carried out using SAS software (SAS Institute, Cary, North Carolina, USA), unless otherwise noted.

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. Informed consent date, first dosing date, country, and investigational site will be presented in a by subject listing of accrual.

7.2.2 Relevant Protocol Deviations

Relevant deviations from the study protocol will be summarized and listed by subjects on the population of all treated subjects.

At entrance:

- Subjects with baseline ECOG Performance Status > 2.
- Subjects with no prior systemic anti-cancer therapy.
- Subjects with no histologically documented stage III or IV melanoma.
- Subjects without measurable disease at baseline.
- Subjects who have not received anti-CTLA-4 therapy or have not progressed on or after anti-CTLA-4 therapy.

On study:

- Subjects receiving concurrent anti-cancer therapy.

Each subject's data will be examined for deviation from protocol criteria (including violation of eligibility criteria, discrepancies between enrolled and treatment received and on-study deviations).

7.3 Study Population

7.3.1 Subject Disposition

Number of subjects enrolled but not treated along with the reason will be tabulated. This analysis will be performed on the enrolled analysis set.

Study participation status including completion and discontinuation of treatment will be reported using the all treated analysis set. Reasons for discontinuation will be summarized and listed.

A subject listing will be provided showing the subject's off study date and reason for going off-study. A subject listing of subjects not treated will also be provided.

7.3.2 Demography and Subject Characteristics

The demographic characteristics, physical measurements, and other baseline characteristics of subjects will be reported using the all treated analysis set, overall and by subpopulations.

The following demographic characteristics, physical measurements, and other baseline characteristics will be summarized. The age of a subject will be defined as the truncated difference in years between the date of the informed consent and the date of birth, plus 1 day (e.g. ((DD/MM/YYYY2 – DD/MM/YYYY1)+1/365.25) = result in years to 1 decimal place (xx.x)).

Frequency and percentage will be reported, unless otherwise noted.

Demographics characteristics:

- Age (< 65; ≥ 65 and < 75; ≥ 75 and < 85; ≥ 65; ≥ 75; ≥ 85; summary statistics) (years)
- Sex (Male, Female)
- Race (White, Black or African American, American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, Other, Not Reported)
- Ethnicity (Hispanic/Latino, Not Hispanic/Latino, Not Reported)

Physical measurements summary:

- Baseline weight (summary statistics) (kg)
- Baseline height (summary statistics) (cm)
- Baseline BMI (summary statistics) (kg/m^2)
- ECOG Performance Status (0-1, 2, Not Reported)

Other baseline characteristics:

- Subtype of Melanoma (Mucosal, Cutaneous, Acral, Ocular/Uveal, Other)
- BRAF Mutation status (Wild type, Mutant, Not Reported)

- Current disease stage (Stage III, Stage IV, Unknown)
- M-stage at study entry (M0, M1A, M1B, M1C, Unknown)
- Brain metastasis (Yes, No)
- Treatment status of CNS metastasis (Treated, Untreated, Leptomeningeal)
- Number of prior therapies (1, 2, >=3)
- Baseline LDH (<=ULN, >ULN, <=2*ULN, >2*ULN)
- Type of autoimmune disorder (Endocrine, Gastrointestinal, Hepatic, Skin, and Other)
- Condition of autoimmune disorder (Active, Not Active)

A subject listing of demography and subject characteristics will be produced on the all treated analysis set.

A summary of demographic characteristics, physical measurements, and other baseline characteristics will also be presented by baseline LDH, BRAF status, and type of autoimmune disorder.

7.3.3 Medical History

A subject listing of general medical history will be produced for all subjects in the treated analysis set.

7.3.4 Disease Characteristics

The following baseline disease characteristics will be summarized using the all treated analysis set by subpopulations:

- Time (in months) from initial pathological diagnosis to first dose of study therapy (summary statistics)
- Baseline tumor assessments (subjects with at least 1 lesion, site of disease, number of disease sites)
- Baseline BRAF, NRAS and cKIT status

A subject listing will be produced on all treated analysis set.

7.3.5 Prior Therapy

The following information will be summarized using the all treated analysis set by subpopulations:

- Prior maintenance therapy (Yes, No, Not Reported)
- On study line of therapy for advance metastatic disease (Second line, Third line, Other)
- Type of prior systemic therapy received (Chemotherapy, Immunotherapy)
- Prior systemic therapy regimen setting (Adjuvant, Neo-adjuvant, Metastatic)
- Best response to most recent prior systemic therapy regimen (CR or PR, SD, PD, Not Reported)
- Time from completion of most recent prior systemic therapy regimen to enrollment (< 3 months, 3-6 months, > 6 months, Not Reported)

- Time from completion of prior adjuvant/neoadjuvant therapy to enrollment (<6 months, >= 6 months, Not Reported)
- Prior surgery related to cancer (Yes, No)
- Prior Radiotherapy (Yes, No)

A listing will be provided using the all treated analysis set. A separate listing will be created for the prior anti-CTLA-4 therapy.

7.3.6 Baseline Examinations

Subjects with abnormal baseline physical exam result will be tabulated by examination criteria (e.g. neck, cardiovascular) using the all treated analysis set by subpopulations.

A listing will be provided using the all treated set.

7.4 Extent of Exposure

The analyses of study drug exposure will focus on the on-study period. The first dosing day corresponds to the day of first administration of any nivolumab. Throughout this analysis plan, dose level will refer to the actual dose rather than the planned dose.

Nivolumab dose reductions and escalations are not permitted.

The nivolumab dose delay and interruption of a subject will be evaluated.

A dose interruption refers to an interruption of the infusion of nivolumab, whether or not the infusion is resumed. If a subject is unable to start a cycle because of unacceptable toxicity related to nivolumab, therapy may be held for up to 6 weeks.

Dose delay, up to 6 weeks, is also allowed for study drug so toxicities return to ≤ Grade 1 or baseline.

If a cycle is delayed, the reason for the delay will be ascertained from the "dosing changes" section of the dosing CRFs.

7.4.1 Administration of Study Therapy

The following parameters will be summarized using the all treated analysis set by subpopulations:

- Number of doses received (1, 2, 3, 4, >4. Summary statistics)
- Cumulative dose (summary statistics)

  The cumulative dose is the sum of the doses (mg/kg) administered to a subject during the treatment period. Dose (mg/kg) is derived based on dose (mg) divided by the most recent body weight (kg) that is collected in the CRF.
- Relative dose intensity (>= 100%, 90% to < 100%, 70% to < 90%, 50% to < 70%, <50%, Not Reported)

  The relative dose intensity is derived as :

  [Cumulative dose (mg/kg) /((Last dose date – Start dose date + 14) x 3/14] x 100
- Duration of therapy (> 3 months, > 6 months, > 9 months, >12 months, summary statistics). A Kaplan-Meier curve will also be presented where the last dose date is the event date for those

subjects who are off study treatment. 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.

7.4.2 Interruption or Delay of Study Therapy

The following parameters will be summarized using the all treated analysis set by subpopulations, according to the general methods:

- Dose interruption (number of subjects with at least one interrupted dose, number of infusion interrupted per subject, reason for interruption, total number of interruptions). The dose interruption information will be retrieved from the CRF dosing pages.
- Dose delay (subjects with at least one delayed dose, number of dose delay per subjects, length of delay: 4-7 days, 8-24 days, 25-42 days, and > 42 days, reason for dose delay, total number of dose delays,). A dose will be considered as delayed if the delay is exceeding 3 days (i.e greater than or equal to 4 days from scheduled dosing date).
- Dose infusion rate reduction (number of subjects with at least one infusion with IV rate reduced, number of infusion with IV rate reduced per subject, reason for IV rate reduction, total number of IV rate reduced). The dose infusion rate reduction information will be retrieved from the CRF dosing pages.

A listing will be provided using the all treated analysis set.

[redacted]

7.4.4 Subsequent Therapy

Subsequent therapy will be summarized using the treated analysis set by subpopulations.

- Number of subjects with any subsequent therapy
- Number of subjects who received subsequent radiotherapy
- Number of subjects who received subsequent surgery
- Number of subjects who received subsequent systemic therapy.

7.5 Efficacy

7.5.1 Overall Survival and Overall Response Rate at Week 12

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.

Overall survival will be summarized using Kaplan-Meier (KM) product-limit method and associated statistics in the all treated analysis set by subpopulations. Median values of OS, if estimable, along with 2-sided 95% CI using the Brookmeyer and Crowley method will be calculated. If medians are not estimable, other percentiles (e.g., 10^{th} and 25^{th}) may be reported. OS

rates at selected time points, including survival rates at 6 months, 12 months, 18 months, and 24 months, together with their 95% CIs will also be estimated using KM estimates on the OS curves. Minimum follow-up must be longer than the timepoint of interest to generate the OS rate for that particular timepoint. For example, if the timepoint of interest is 6 months and the interval of enrollment date and last patient last visit is less than 6 months, then, the minimum follow-up is not reached and OS rate is not generated. Associated 2-sided 95% CIs will be calculated using the Greenwood formula.

A swimming plot showing the response, progression, duration of therapy and death will be presented using the all treated analysis set, overall and by ECOG PS 2, Ocular/Uveal, and Mucosal subpopulations only.

The overall response rate is defined as the number of subjects with a complete response (CR) or partial response (PR) at week 12 divided by the number of subjects treated. The overall response will be summarized by binomial response rates and their corresponding two-sided 95% exact CIs using the Clopper-Pearson method. A by subject listing will be provided.

A summary of overall response will also be presented by baseline LDH, BRAF status, and type of autoimmune disorder.

7.5.2 Subject Follow-up for OS

Overall Survival probabilities for each subpopulations will be estimated and plotted using the Extent of follow-up defined as the time between first dose date and last known date alive (for subjects who are alive) or death date (for subjects who died) will be summarized descriptively (median, min, max) for all subjects treated.

The currentness of follow-up, defined as the time between last OS contact (ie, last known date alive or death date) and data cut-off date, will be summarized by subpopulations. Subjects who died before data cut-off date will automatically have zero value for currentness of follow-up. For subjects with last known date alive after data cut-off date, they will have zero value for currentness of follow-up as well. The currentness of follow-up will be categorized into the following categories: 0 days, 1-30 days, 31-60 days, 61-90 days, 91-120 days, 121-150 days, 151 or more days.

7.5.3 Subgroups Analyses

OS among treated population will also be summarized within subsets at baseline (with two-sided 95% CI for the medians calculated via log-log transformation.).

- Age (< 65, ≥ 65)
- Gender (male, female)
- M-Stage at diagnosis
- Number of lines of prior systemic treatment in metastatic setting (add footnote for only metastatic setting)
- Baseline LDH (<= ULN, >ULN, >2xULN)

7.6 Safety

Unless otherwise specified, safety results will be presented using the all treated analysis set subjects by subpopulations. See Core Safety SAP for more details on safety analysis.

7.6.1 Primary Analysis

7.6.1.1 High-grade (CTCAE v4.0 Grade 3 or higher) Treatment-Related, Select Adverse Events.

The number and percentage of subjects who report high-grade (CTCAE v4.0 Grade 3 or higher), treatment-related, select adverse events pulmonary, gastrointestinal, skin, renal, hepatic, pancreatic, neurologic, endocrine) will be summarized using the all treated analysis set by system organ class and Medical Dictionary for Regulatory (MedDRA) preferred term. In addition, the number, percentage of subjects, 95% CI for the percentage of subjects with these select AEs will also be presented by subpopulations.

7.6.2 Secondary Analysis

7.6.2.1 High-grade (CTCAE v4.0 Grade 3 or higher) Select Adverse Events

The number and percentage of subjects who report high-grade (CTCAE v4.0 Grade 3 or higher), select adverse events will be summarized using the all treated analysis set by system organ class and Medical Dictionary for Regulatory (MedDRA) preferred term.

7.6.2.2 Select Adverse Events

Select adverse events 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 Core Safety SAP.

7.6.3 Other Safety Analysis

Other safety analysis will be conducted as below as specified in the Core Safety SAP, according to the general methods:

- Deaths
- Serious adverse events
- Adverse events leading to discontinuation of study therapy
- Adverse events leading to dose modification
- Adverse events
- Multiple adverse events
- Laboratory parameters
- Vital signs
- Pregnancy
- Adverse events by demographic subgroups

A summary by type of autoimmune disorder will be presented for the following adverse events tables.

- Any adverse events
- Drug-related adverse events
- Drug-related serious adverse events
- Drug-related adverse events leading to discontinuation
- Drug-related select adverse events
- Drug-related select adverse events leading to discontinuation
- Any adverse events that required immune modulating medications
- Time to resolution of drug-related select adverse events
- Time to resolution of drug-related select adverse events where immune modulating medications was initiated
- Time to onset of drug-related select adverse events

[redacted]

A subject listing of prior immune modulating medications (subjects with any prior immune modulating medication, subjects by medication class and generic term) will be presented. This would include immune modulating medications taken on or before first dose of study therapy.

7.6.4 Immunogenicity Analysis

Not applicable

[redacted]

7.8 Outcomes Research Analyses

Outcomes research (Quality-of-life) data will be measured using the EORTC QLQ-C30 and EQ-5D-3L questionnaires. The analysis of EORTC QLQ-C30 and EQ-5D-3L will be restricted to treated subjects who have an assessment at baseline and at least one post-baseline assessment.

7.8.1 EORTC QLQ-C30

For EORTC QLQ-C30, all scales and single items are scored on categorical scales and linearly transformed to 0-to-100 scales with higher scores for a functional scale representing higher levels of functioning, higher scores for the global health status/quality of life scale representing higher levels of global health status/quality of life and higher scores for a symptom scale representing higher level of symptoms. A score difference of 10 is used as an estimate of a clinically important difference for the scales of the EORTC QLQ-C30[5].

The following descriptive analyses will be conducted:

- EORTC QLQ-C30 questionnaire completion rate, defined as the proportion of questionnaires actually received out of the expected number (i.e., number of subjects on treatment or in follow up) will be calculated and summarized for each assessment time point by treatment group.

- Mean score and mean change from baseline in EORTC QLQ-C30 global health status, functional scales and symptom scales will be summarized using descriptive statistics (N, mean with SD and 95% CI, median, first and third quartiles, minimum, maximum) for all scales at each assessment time point.
- A line graph summarizing the mean changes from baseline will be produced for all scales.

7.8.2 EuroQoL Five Dimensions Questionnaire

The following descriptive analyses will be conducted:

- EQ-5D-3L questionnaire completion rate, defined as the proportion of questionnaires actually received out of the expected number (i.e. number of subjects on treatment or in follow up), will be calculated and summarized for each assessment time point by treatment group.
- A by-subject listing of the level of problems in each dimension, corresponding to EQ-5D-3L health state (i.e., 5-digit vector), EQ-5D-3L utility index score, and EQ-5D-3L VAS score will be provided.
- Proportion of subjects reporting problems for the 5 EQ-5D-3L dimensions at each assessment time point will be summarized by level of problem and by treatment group. Percentages will be based on number of subjects assessed at assessment time point.
- For the EQ-5D-3L utility index and VAS scores, separately:
  - Mean score and mean change from baseline at each assessment time point will be summarized by treatment group using descriptive statistics (N, mean with SD and 95% CI, median, first and third quartiles, minimum, maximum).
  - A line graph summarizing the mean changes from baseline will be produced.

8 CONVENTIONS

Unless otherwise noted, the following conventions should be understood to apply. Further conventions may be detailed in the Data Presentation Plan (DPP).

8.1 Baseline

Baseline results will be the last non-missing result occurring prior to the first dose of treatment medication.

8.2 Duration, On-study Event calculations

The duration between two dates will be calculated as [later date] – [earlier date] + 1 day. Study Day 1 or first dose date is the date of first study medication. Study day associated with an assessment will be calculated as [assessment date] – [first dose date (or enrollment date for non-treated subjects)], if the assessment is before first dose/enrollment; [assessment date] – [first dose date (enrollment for non-treated subjects] + 1, if the assessment is on or after first dose/enrollment.

Events will be considered as occurring within X days (e.g., deaths within 30 days, deaths and AEs within 90 days) of last dose of study medication if [event date] – [last dosing date] ≤ X.

The following factors will convert days to months or years: 1 month = 30.4375 days, 1 year = 365.25 days.

8.3 Conventions for Partial/Missing Dates

Unless specified otherwise the following conventions will be used for imputing partial dates:

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

For date of death:

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day*.
- If both the day and the month are missing, "Jan 1" will be used to replace the missing information*.
- If date is missing, death date will be imputed as the last known alive date.
  * The imputed death date will be compared with the last known alive date (date of censoring for survival). If the death date is not equal to the date of censoring for survival then the maximum of the (imputed death date, date of censoring for survival) will be considered as the date of death.

For date of progression:

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day*.
- If the day and month are missing or a date is completely missing, it will be considered as missing.
  * In case, the date of death is present (complete date), the imputed progression date will be compared with the date of death. The minimum of the (imputed progression date, date of death) will be considered as the date of progression.

For date of last tumor assessment:

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day*
- If the day and month are missing or a date is completely missing, it will be considered as missing.
  * In case, the date of death is present (complete date), the imputed date will be compared with the date of death. The minimum of the (imputed date, date of death) will be considered as the date of last tumor assessment.

For adverse events of special interest onset date:

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

For adverse events of special interest resolution date:

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

Otherwise, missing values will not in general be imputed.

8.4 Missing Data

No imputation method will be implemented for any missing items. The planned outcomes research analyses will be based on all available data points collected during the course of the study.

For the EORTC QLQ-C30, values will be imputed for missing items by using values equal to the average of the non-missing items for any scale in which at least half the items are completed. A scale in which fewer than half of the items are completed will be treated as missing.

Once instrument data are scored, no imputation will be used to handle missing data. In the longitudinal model, imputing missing data may lead to underestimating the variance of treatment effects over time and unintentional biasing of estimates. Once the type and source of missing data observed is evaluated (e.g., missing at random [MAR], missing completely at random [MCAR], missing not at random [MNAR]), appropriate measure will be taken to handle missing data. Recommended statistical approaches to handling missing data particularly for longitudinal studies involve generalized linear mixed models when the data are MAR or MCAR. Realistically, since once cannot rule out MNAR in clinical trial longitudinal data, a pattern mixture model will be employed to investigate the possibility of MNAR. Mixed models are seen as an unbiased estimate under MAR conditions, and pattern mixture models are a method for identifying missing data as MAR or MNAR, as well as meaning behind the missing data. If the worst case analysis provides similar results to the model with no missing data imputed, then the results from the original model are likely robust to missing data.

9 CONTENT OF REPORTS

Study reports will be written corresponding to the final analyses of OS. The table, figure and listing outputs that will be produced will be described in the Data Presentation Plan for the study.

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. pituitary disorders, diabetes, thyroid disorders, 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 5 using MedDRA version 18.1. 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, endocrine adverse event, hepatic adverse event, hypersensitivity/infusion reaction, renal adverse event, skin adverse event) 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 5) 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 4 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 4: 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 5: Select Adverse Events

Category	Subcategory	Preferred Term
ENDOCRINE ADVERSE EVENT	ADRENAL DISORDER	ADRENAL INSUFFICIENCY
		ADRENAL SUPPRESSION
		ADRENOCORTICAL INSUFFICIENCY ACUTE
		BLOOD CORTICOTROPHIN DECREASED
		BLOOD CORTICOTROPHIN INCREASED
		HYPOTHALAMIC PITUITARY ADRENAL AXIS SUPPRESSION
		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

Table 5: Select Adverse Events

Category	Subcategory	Preferred Term
		PRIMARY HYPERTHYROIDISM
		PRIMARY HYPOTHYROIDISM
		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
		COLITIS ULCERATIVE
		DIARRHOEA
		ENTERITIS
		ENTEROCOLITIS
		FREQUENT BOWEL MOVEMENTS
		GASTROINTESTINAL PERFORATION
HEPATIC ADVERSE EVENT		ACUTE HEPATIC FAILURE
		ACUTE ON CHRONIC LIVER FAILURE
		ALANINE AMINOTRANSFERASE INCREASED

Table 5: Select Adverse Events

Category	Subcategory	Preferred Term
		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

Table 5: Select Adverse Events

Category	Subcategory	Preferred Term
PULMONARY ADVERSE EVENT		ACUTE RESPIRATORY DISTRESS SYNDROME
		ACUTE RESPIRATORY FAILURE
		INTERSTITIAL LUNG DISEASE
		LUNG INFILTRATION
		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

Table 5: Select Adverse Events

Category	Subcategory	Preferred Term
		DRUG ERUPTION
		ECZEMA
		ERYTHEMA
		ERYTHEMA MULTIFORME
		EXFOLIATIVE RASH
		FIXED DRUG ERUPTION
		NODULAR RASH
		PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME
		PHOTOSENSITIVITY REACTION
		PRURITUS
		PRURITUS ALLERGIC
		PRURITUS GENERALISED
		PSORIASIS
		RASH
		RASH ERYTHEMATOUS
		RASH GENERALISED
		RASH MACULAR
		RASH MACULO-PAPULAR
		RASH MORBILLIFORM
		RASH PAPULAR
		RASH PRURITIC
		RASH VESICULAR
		SKIN EXFOLIATION

Table 5: Select Adverse Events

Category	Subcategory	Preferred Term
		SKIN HYPOPIGMENTATION
		SKIN IRRITATION
		STEVENS-JOHNSON SYNDROME
		TOXIC EPIDERMAL NECROLYSIS
		TOXIC SKIN ERUPTION
		URTICARIA
		VITILIGO

Source: MedDRA version 18.1

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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