STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

A PHASE 1/2 STUDY TO EVALUATE THE PHARMACOKINETICS, PHARMACODYNAMICS, SAFETY, AND TOLERABILITY OF BMS-986205 ALONE AND IN COMBINATION WITH NIVOLUMAB IN CHINESE PATIENTS WITH ADVANCED MALIGNANT SOLID TUMORS

PROTOCOL CA017076

VERSION # 1.0

DATE: 06-Oct-2021

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[redacted]

2 STUDY DESCRIPTION

2.1 Study Design

This is a Phase 1/2, open-label study of BMS-986205 administered as a monotherapy and in combination with nivolumab in participants with advanced malignant solid tumors.

Treatment will start with a 2-week monotherapy lead-in (Cycle 0) whereby BMS-986205 100 mg oral daily dose must be administered with a meal at approximately the same time each day.

Participants will then proceed to receive the combination of nivolumab and BMS-986205. Nivolumab will be administered at a dose of 480 mg IV Q4W.

Cycle 0

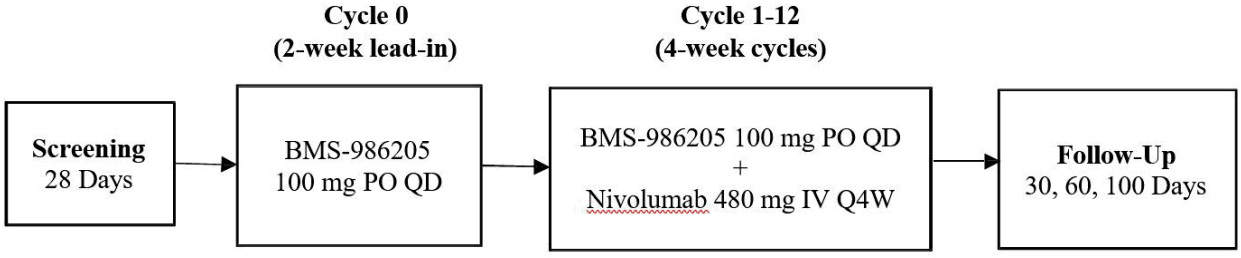
Participants will start with Cycle 0, which is a 2-week BMS-986205 monotherapy lead-in, with a 100-mg oral daily dose. Participants who have received at least 75% of doses in Cycle 0 will be eligible to proceed to receive the combination of nivolumab and BMS-986205 (Cycle 1).

The following AEs will prohibit a participant from proceeding to combination with nivolumab (Cycle 1):

- Grade 2 or higher immune-related AEs (irAEs) considered related to BMS-986205 (eg, immune-mediated pneumonitis, colitis, hepatitis, nephritis, and renal dysfunction) with the exception of immune-mediated hypothyroidism and hyperthyroidism
- Grade 2 AST and ALT elevations that do not resolve to Grade 1 or baseline within 1 week
- ≥ Grade 3 elevation of AST, ALT, or total bilirubin that persists for ≥ 7 days
- Grade 2 AST or ALT elevation with symptomatic liver inflammation (eg, right upper quadrant tenderness, jaundice, pruritus)
- AST or ALT > 3× upper limit of normal (ULN) and concurrent total bilirubin > 2× ULN without initial findings of cholestasis (elevated serum alkaline phosphatase, eg, findings consistent with Hy's law or FDA definition of potential drug-induced liver injury [DILI])
- Grade 2 or greater episcleritis, uveitis, or iritis
- Any other Grade 2 eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks OR requires systemic treatment
- Grade 3 or greater uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
- Any Grade 3 or greater non-dermatologic, non-hepatic, non-hematologic toxicity with the following specific EXCEPTIONS:
  - Grade 3 or Grade 4 electrolyte abnormalities that are not complicated by associated clinical adverse experiences, last less than 48 hours and either resolve spontaneously or respond to conventional medical intervention
  - Grade 3 nausea, vomiting, or diarrhea that lasts less than 48 hours, and either resolves spontaneously or responds to conventional medical intervention
  - Isolated Grade 3 elevation of amylase or lipase not associated with clinical or radiographic evidence of pancreatitis
  - Isolated Grade 3 fever not associated with hemodynamic compromise (eg, hypotension, clinical or laboratory evidence of impaired end-organ perfusion)
  - Grade 3 endocrinopathy that is well-controlled by hormone replacement
  - Grade 3 tumor flare (defined as pain, irritation, or rash that localizes to site of known or suspected tumor)
  - Grade 3 fatigue
- Grade 3 rash if no improvement (ie, resolution to ≤ Grade 1) after a 1- to 2-week dose delay.
- Grade 4 rash of any duration
- Methemoglobin levels ≥ 15% and study-drug related
- Grade 4 neutropenia ≥ 5 days in duration and study-drug related
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding (study-drug related), or any requirement for platelet transfusion (study-drug related)
- Grade ≥ 3 febrile neutropenia for 48 hours, study-drug related
- Grade ≥ 3 hemolysis (ie, requiring transfusion or medical intervention such as steroids), study-drug related
- Grade 4 anemia not explained by underlying disease (study-drug related)

A schematic of the study is provided in Figure 2.1-1.

Figure 2.1-1: Study Schematic



Treatment may continue from Cycle 0 (2 weeks) until 50 weeks (or up to a total maximum of 98 weeks if applicable), disease progression, or withdrawal of consent.

In addition, cohort may be expanded in this study to gather additional safety, tolerability, PK, pharmacodynamics, and preliminary efficacy information regarding BMS-986205 in combination with nivolumab in certain tumor type(s).

Participants will complete up to 3 phases of the study: Screening, Treatment, and Clinical/Safety Follow-up, as described below.

Screening

The screening phase will last for up to 28 days. Screening begins by establishing the participant's initial eligibility and signing the informed consent form (ICF).

Treatment

The treatment phase consists of the 2-week monotherapy lead-in (Cycle 0) and up to twelve 4-week combination therapy cycles. The 2-week lead-in treatment consists of a single oral daily dose of BMS-986205. The combination therapy cycles are comprised of an oral daily dose of BMS-986205 and one dose of nivolumab administered intravenously Q4W on Day 1 of each treatment cycle up to 12 cycles. Total study treatment period is up to 50 weeks.

Following every two combination therapy treatment cycles (8 weeks) starting with Cycle 1, the decision to treat a participant with additional cycles of study therapy will be based on radiological tumor assessments (initial evaluation performed at baseline, end of Cycle 2, and every 8 weeks). Assessments of PR and CR must be confirmed at least 4 weeks following initial assessment. Tumor progression or response endpoints will be assessed using RECIST v1.1 criteria for solid tumors (Appendix 5 in protocol).

Treatment beyond progression may be allowed in select participants with initial RECIST v1.1 disease progression (PD) after discussion and agreement with the BMS medical monitor (with proper documentation in the Trial Master File) that the benefit/risk assessment favors continued administration of study therapy (eg, participants are continuing to experience clinical benefit as

assessed by the investigator, tolerating treatment, and meeting other criteria specified in in protocol Section 8.1.2).

Participants with a response of stable disease (SD), PR, or CR at the end of a given cycle will continue to the next treatment cycle. Participants will generally be allowed to continue study therapy until the first occurrence of either: 1) completion of the maximum number of 12 cycles; 2) PD; 3) clinical deterioration suggesting that no further benefit from treatment is likely; 4) intolerability to therapy; or 5) the participant meets criteria for discontinuation of study therapy as outlined in protocol Section 7.4.4. Individual participants with confirmed CR will be given the option to discontinue study therapy on a case-by-case basis after specific consultation and agreement between the investigator and BMS medical monitor in settings where benefit/risk justify discontinuation of study therapy.

In all parts of this study, all participants will be treated for 48 weeks of BMS-986205 in combination with nivolumab unless criteria for study drug discontinuation are met earlier (protocol Section 7.4.4). All participants completing approximately 48 weeks of combination study therapy with ongoing disease control (CR, PR, or SD) may be eligible for an additional 48 weeks of study therapy at the originally assigned dose regimen beyond the initial 48 weeks, on a case-by-case basis, after careful evaluation and discussion with the BMS medical monitor to determine whether the benefit/risk ratio supports administration of further study drug. Subjects whose last assessment of the initial 48-week period shows PD will also be eligible to continue to additional cycles if they are still deriving clinical benefit, as per the guidance of treatment beyond progression (protocol Section 8.1.2). Upon completion of 48 weeks of combination treatment (or up to a maximum of 96 weeks if applicable), all subjects will enter the Clinical/Safety Follow-Up period.

Clinical/Safety Follow-Up

Upon completion of 48 weeks of combination treatment (or up to a maximum of 96 weeks if applicable), all participants will enter the Clinical/Safety Follow-Up period after the decision is made to discontinue the participant from treatment (eg, at end of treatment [EOT]).

For participants who complete all scheduled cycles of therapy, the EOT visit will be the same as the last scheduled and completed on-treatment visit, and the start of the Week 1 Clinical/Safety Follow-Up visit. For participants who do not complete all scheduled cycles of therapy, the EOT visit will be the most recent on-treatment visit (with all available safety and response data) and does not need to be repeated, and will be considered the start of the Week 1 Clinical/Safety Follow-Up visit.

Participants who discontinue the treatment phase will enter the Clinical/Safety Follow-Up period. Participants must be followed for at least 100 days after the last dose of study therapy or 30 days if participant only received BMS-986205. Follow-up visits should occur at Days 30, 60, and 100 (± 10 days) after the last dose of study therapy or should coincide with the date of discontinuation (± 10 days) if date of discontinuation is greater than 30 days after the last dose of study therapy to monitor for AEs. All participants will be required to complete one (if participant only received BMS-986205) or three Clinical/Safety Follow-Up visits regardless of whether they start a new anti-cancer therapy, except those participants who withdraw consent for study participation.

2.2 Treatment Assignment

The subject must be enrolled into the study after the subject's eligibility is established and informed consent has been obtained. The study treatments include BMS-986205 and BMS-936558 (nivolumab). Subjects will be treated at dose level as specified in Section 2.1.

2.3 Blinding and Unblinding

This is an open-label study.

2.4 Protocol Amendments

This analysis plan reflects Revised Protocol 01, dated 18-Oct-2018.

3 OBJECTIVES

3.1 Primary

The primary objective of this study is to characterize the PK and assess the safety and tolerability of BMS-986205 administered alone and in combination with nivolumab in Chinese participants with advanced malignant tumors.

3.2 Secondary

- To characterize the pharmacodynamic activity of BMS-986205 administered alone and in combination with nivolumab.
- To characterize the immunogenicity of nivolumab when administered in combination with BMS-986205.
- To investigate the preliminary anti-tumor activity of BMS-986205 administered in combination with nivolumab in advanced malignant tumors.

4 ENDPOINTS

Endpoints to address the objectives in Section 3 are reflected in Table 4-1.

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
• The primary objective of this study is to characterize the PK and assess the safety and tolerability of BMS-986205 administered alone and in combination with nivolumab in Chinese participants with advanced malignant tumors.	• PK parameters; Incidence of AEs, SAEs, AEs leading to discontinuation, deaths, and laboratory abnormalities.
The secondary objectives of this study are: • To characterize the pharmacodynamic activity of BMS-986205 administered alone and in combination with nivolumab. • To characterize the immunogenicity of nivolumab when administered in combination with BMS-986205. • To investigate the preliminary anti-tumor activity of BMS-986205 administered in combination with nivolumab in advanced malignant tumors.	• Incidence of anti-drug antibodies (ADA) to nivolumab; measurement of serum kynurenine and tryptophan levels. • ORR, best overall response (BOR) and duration of response (DOR) as assessed per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 by investigator.

4.1 Efficacy Endpoints

4.1.1 Objective Response Rate

Objective Response Rate (ORR) is defined as the number of treated subjects who achieve a best response of confirmed complete response (CR) or confirmed partial response (PR) based on investigator assessments (using RECIST v1.1 criteria) divided by the number of all treated subjects.

Best Overall Response (BOR) is defined as the best response, as determined by the investigator, recorded between the date of first dose and the date of objectively documented progression per RECIST v1.1 criteria or the date of subsequent therapy (including tumor-directed radiotherapy and tumor-directed surgery), whichever occurs first. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR determination. Confirmation of response is required at least 4 weeks after the initial response.

4.1.2 Duration of Response

Duration of Response (DOR) is defined as the time between the date of first confirmed documented response (CR or PR) to the date of the first documented tumor progression as determined by the investigator (per RECIST v1.1 criteria), or death due to any cause, whichever occurs first. Subjects who start subsequent therapy without a prior reported progression will be censored at the last evaluable tumor assessments prior to initiation of the subsequent anticancer therapy. Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who neither progress nor die, DOR will be censored on the date of their last evaluable tumor assessment. DOR will be evaluated for responders (confirmed CR or PR) only.

4.2 Safety Endpoints

The assessment of safety will be based on the incidence of adverse events (AEs), serious adverse events (SAEs), adverse events leading to discontinuation, adverse events leading to dose modification (i.e. dose delay/reduction), select adverse events (select AEs) for EU/ROW Submissions, immune-mediated AEs (IMAEs) for US Submission, [redacted] and deaths. The use of immune modulating concomitant medication will be also summarized. In addition clinical laboratory tests, and immunogenicity (i.e. development of anti-drug antibody) will be analyzed.

4.3 Other Endpoints

4.3.1 Pharmacokinetics

PK will be determined from BMS-986205/select metabolites plasma and urine for %UR24 and nivolumab serum concentrations. Samples will be collected to characterize pharmacokinetics and to explore exposure-safety and exposure-efficacy relationships.

Selected BMS-986205 parameters, such as Cmax, Tmax, AUC(TAU), Ctrough, T-HALF(T-HALFeff_AUC), CLT/F, Accumulation index (AI), %UR24, and selected BMS-986205 metabolites parameters, such as Cmax, Tmax, AUC(TAU), Ctrough, %UR24, MR_Cmax,

MR_AUC(TAU), will be assessed from concentration-time data during BMS-986205 monotherapy and combination phase (Part 1 and Part 2).

End-of-infusion (Ceoi) and trough (Ctrough) concentrations for nivolumab will be assessed during combination phase (Part 2).

PK parameters will be provided by the CPAR group.

[redacted]

4.3.3 Immunogenicity

Serum samples collected for anti-drug antibodies against nivolumab will be analyzed by a validated immunogenicity assay.

In addition, ad hoc serum samples designated for pharmacokinetic assessments may also be used for immunogenicity analysis if required (e.g., insufficient volume for complete immunogenicity assessment or to follow up on suspected immunogenicity related AE).

Further details on immunogenicity [redacted] definitions, population for analyses and endpoints are described in APPENDIX 2.

[redacted]

4.3.5 Pharmacodynamics

Change from baseline for serum kynurenine and tryptophan and corresponding percent change from baseline will be assessed.

5 SAMPLE SIZE AND POWER

The sample size for this study is not based on statistical power, but based on consideration of the precision of the estimate of geometric means of Cmax and AUC of BMS-986205. Based on preliminary PK results from Study CA017003 cohorts 25 mg to 200 mg, assuming the inter-subject CV for AUC24 is 42%, a sample size of 12 PK evaluable subjects will be sufficient for the point estimates of the mean PK parameter to fall within 80% to 125% of the true value, with 91% confidence level. Assuming the inter-subject CV for Cmax is 29%, a sample size of 12 PK evaluable subjects will be sufficient for the point estimates of the mean PK parameter to fall within 80% to 125% of the true value, with 98% confidence level. Twelve subjects will provide 90% probability of observing at least one occurrence of a specific AE that would occur with an 18% incidence in the population.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

- Baseline period:
  - Baseline evaluations or pre-treatment events will be defined as evaluations or events that occur before the date and time of the first dose of study treatment. Evaluations (laboratory tests, pulse oximetry, vital signs) on the same date and time of the first dose of study treatment will be considered as baseline evaluations. Events (AEs) on the same date and time of the first dose of study treatment will not be considered as pre-treatment events.
  - In cases where the time (onset time of event or evaluation time and dosing time) is missing or not collected, the following definitions will apply:
    - Pre-treatment AEs will be defined as AEs with an onset date prior to but not including the day of the first dose of study treatment;
    - Baseline evaluations (laboratory tests, pulse oximetry, vital signs) will be defined as evaluations with a date (and time if collected) on or prior to the date of first dose of study treatment.
  - If there are multiple valid observations in the baseline period, then the latest non missing observation will be used as the baseline in the analyses. If multiple observations exist on the latest collection date (and time if collected), the record with the latest data entry date and time will be used. If multiple observations exist on the latest collection date (and time if collected) and data entry date and time, then the first observation is used as baseline, unless otherwise specified.
- For nivolumab Anti-Drug Antibody (ADA), the baseline record ofIDO1 inhibitor immunogenicity (IMG) evaluation must be less than the date and time of the first NivolumabIDO1 inhibitor dose date and time.
- Post baseline period:
  - On-treatment AEs will be defined as AEs with an onset date and time on or after the date and time of the first dose of study treatment (or with an onset date on or after the day of first dose of study treatment if time is not collected or is missing). For subjects who are off study treatment, AEs will be included if event occurred within a safety window of 100 days after the last dose of study treatment if a participant received BMS-986205 + NIVO (or 30 days after the last dose of study treatment if a participant received only BMS-986205). No "subtracting rule" will be applied when an AE occurs both pre-treatment and post-treatment with the same preferred term and grade.
  - On-treatment evaluations (laboratory tests, pulse oximetry and vital signs) will be defined as evaluations taken after the day (and time, if collected and not missing) of first dose of study treatment. For subjects who are off study treatment, evaluations should be within a safety window of 100 days after the last dose of study treatment if a participant received BMS-986205 + NIVO (or 30 days after the last dose of study treatment if a participant received only BMS-986205).

- Post baseline period by phase:
  - Mono lead-in period starts with the first dose of BMS986205 and end prior to first dose of nivolumab.
    - Mono lead-in AEs will be defined as AEs with an onset date and time on or after the date and time of the first dose of initial mono study treatment (or with an onset date on or after the day of first dose of initial mono study treatment if time is not collected or is missing) and prior to the date-time of the first dose of nivolumab (or with an onset date prior to the day of first dose of nivolumab if time is not collected or is missing). For subjects who discontinue during Mono lead in, AEs will be included if event occurred within a safety window of 30 days after the last dose of BMS-986205 initial mono study treatment. No "subtracting rule" will be applied when an AE occurs both pre-treatment and post-treatment with the same preferred term and grade.
    - Mono lead-in evaluations (laboratory tests, pulse oximetry and vital signs) will be defined as evaluations taken after the day and time of the first dose of initial mono study treatment (or with a start date after the day of first dose of initial mono study treatment if time is not collected or is missing) and prior to the date-time of the first dose of nivolumab (or with a start date on or prior to the day of first dose of nivolumab if time is not collected or is missing). For subjects who discontinue during Mono lead in, evaluations will be included if evaluation is taken within a safety window of 30 days after the last dose of BMS-986205 initial mono study treatment.
  - Combination Treatment Period starts with the first dose date-time of initial nivolumab.
    - Combination treatment AEs will be defined as AEs with an onset date and time on or after the date and time of the first dose of nivolumab (or with an onset date on or after the day of first dose of nivolumab if time is not collected or is missing). For subjects who are off study treatment, AEs will be included if event occurred within a safety window of 100 days after the last dose of study treatment.
    - Combination treatment evaluations (laboratory tests, pulse oximetry and vital signs) will be defined as evaluations taken after the day (and time, if collected and not missing) of first dose of nivolumab. For subjects who are off treatment, evaluations will be included if evaluation is taken within 100 days of the last dose of study medication.

6.2 Treatment Regimens

Refer to Table 6.2-1 for treatment regimens explored in this trial:

Table 6.2-1: Treatment Regimen Information

Phase	Treatment Regimen Description
Lead-in	BMS-986205 100 mg PO QD
Combination	BMS-986205 100 mg PO QD + Nivolumab 480 mg IV Q4W

6.3 Populations for Analyses

- Enrolled subjects Population: All subjects who signed the informed consent form and obtained a subject number.
- Treated subjects Population: All enrolled subjects who received at least one dose of any study treatment.
- Pharmacokinetic Population: All enrolled subjects who received at least one dose of any study treatment and have any available concentration-time data.
- Evaluable Pharmacokinetic Population: A subset of the PK Population, defined as all subjects who have adequate PK profiles or have at least one evaluable PK parameter. All available derived PK parameter values will be included in the PK data set and reported, but only participants with evaluable PK will be included in the summary statistics.
- Immunogenicity Population: All enrolled subjects who received at least one dose of nivolumab and have a baseline and at least one post-treatment immunogenicity measurement.

Unless otherwise specified, the safety analyses will include all treated subjects.

Unless otherwise specified, the efficacy analyses will include all treated subjects.

7 STATISTICAL ANALYSES

All analyses will be performed in SAS using version 9.3 or higher and S-Plus for some figures.

7.1 General Methods

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

Time-to-event variables (e.g., time-to resolution) will be analyzed using the Kaplan-Meier technique. When specified, the median will be reported along with 95% CI using Brookmeyer and Crowley method[1] (using log-log transformation for constructing the confidence intervals[2]).

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

7.1.1 Adverse Events, Serious Adverse Events, Multiple events, Select Adverse Events, [redacted] and Immune-Mediated Adverse Events

Drug-related AEs are those events with relationship to study drug "Related", as recorded on the CRF. If the relationship to study drug is missing, the AE will be considered as drug-related.

Serious adverse events consist of AEs deemed serious by the Investigator and flagged accordingly in the CRF and clinical database.

Adverse events leading to study drug discontinuation are AEs with action taken regarding study drug(s) = "Drug Withdrawn".

Adverse events leading to dose delay are AEs with action taken regarding study drug(s) = "Dose Delayed".

Adverse events leading to dose reduction are AEs with action taken regarding study drug(s) = "Dose Reduced".

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and the most recent version of the dictionary at the time of the database lock will be used. Adverse event results will be graded for severity using the NCI Common Terminology Criteria for Adverse Events (CTCAE) and the version of the criteria specified in the protocol will be used.

In the AE summary tables, unless otherwise specified, subjects will be counted only once at the Preferred Term (PT), only once at the System Organ Class (SOC), and only once at subject level for the counting of total number of subjects with an AE. The AE tables will be sorted by the SOCs and then PTs. SOC will be ordered by descending frequency overall and then alphabetically. PTs will be ordered within SOC by descending frequency overall and then alphabetically. The sorting will be done based on the 'Any Grade' column.

Unless otherwise specified, the AE summary tables will be restricted to on-treatment events regardless of the causality.

Analyses that take into account the multiple occurrences of a given adverse event will be conducted (see Section 7.6.9). To prepare these analyses, the CRF data will be processed according to standard BMS algorithms[3] in order to collapse adverse event records into unique records based on the preferred term.

[redacted]

7.1.1.3 Immune-Mediated Adverse Events (US Submission)

In order to further characterize AEs of special clinical interest, analysis of immune-mediated AEs (IMAE) will be conducted. IMAEs are specific events (or groups of PTs describing specific events) that include pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, endocrine (adrenal insufficiency, hypothyroidism/thyroiditis, hypothyroidism, thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis), and other specific events, considered as potential immune-mediated events by investigator that meet the definition summarized below:

- those occurring within 100 days of the last dose
- regardless of causality
- treated with immune-modulating medication (of note, endocrine AEs such as adrenal insufficiency, hypothyroidism/thyroiditis, hypothyroidism, thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis are considered IMAEs regardless of immune-modulating medication use, since endocrine drug reactions are often managed without immune-modulating medication)
- with no clear alternate etiology based on investigator assessment, or with an immune-mediated component

The list of MedDRA preferred terms used to identify IMAEs is revisited quarterly and updated accordingly. The preferred terms used for the selection at the time of the database lock by categories will be provided.

7.1.2 Laboratory Tests

Clinical laboratory parameters (hematology, serum chemistry and electrolytes) will be evaluated.

Laboratory tests will be graded using the NCI Common Terminology Criteria, and the most recent version of the criteria at the time of the database lock will be used.

Clinical laboratory data will be first analyzed using International System of Units (SI).

Analyses will be repeated using US conventional units.

In the laboratory summary tables, unless otherwise specified, subjects will be counted only once for each lab parameter according to their worst on treatment CTC grade (worst being the highest CTC grade). The laboratory tables and listings will be sorted by laboratory category, laboratory subcategory and laboratory test code sequence number.

7.1.3 Immunogenicity data

Blood samples for nivolumab immunogenicity analysis will be collected according to the protocol schedule. Samples will be evaluated for development of Anti-Drug Antibody (ADA) by a validated electrochemiluminescent (ECL) immunoassay.

7.2 Study Conduct

Non-programmable relevant eligibility and on-treatment, as well as significant (both programmable and/or non-programmable) protocol deviations will be reported through [redacted] listings.

Enrollment by country and site will be summarized and listed for all enrolled subjects.

A by-subject listing of batch numbers for all treated subjects will be provided.

7.3 Study Population

Analyses in this section will be tabulated for all treated subjects, unless otherwise specified.

7.3.1 Subject Disposition

Subject Pre-treatment Status

The total number of subjects enrolled (entering or not entering treatment period) will be presented along with the reason for not entering treatment period. This analysis will be performed on the all enrolled subjects population only.

Reason for not entering treatment period will be derived from subject status CRF page.

A by-subject listing including the above information will also be provided for all enrolled subjects.

Subject Phase Status

Number of ongoing, completed and discontinued subjects along with discontinuation reason and next expected study phase will be summarized on the all treated subjects population for the following:

- Mono lead-in
- Combination
- Follow-up (excluding next expected study phase)

Reason for discontinuation will be derived from subject status CRF page.

A by-subject listing including the above information will also be provided for all treated subjects.

Subject Completion Status

Number of subjects of the following along with discontinuation reason will be summarized on the all treated subjects population:

- Ongoing
- Completed the study
- Discontinued the study
- Reason for discontinuation will be derived from subject status CRF page.

A by-subject listing including the above information will also be provided for all treated subjects.

7.3.2 Demographics and Other Baseline Disease Characteristics

The following demographic and baseline disease characteristics will be summarized and listed:

- Age (continuous)
- Age categorization (< 65, ≥ 65)
- Sex (Male vs. Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Asian Indian, Chinese, Japanese, Malay, Asian Other, Other)
- Height
- Baseline Weight
- Baseline ECOG performance status
- Smoking History (Current/Former, Never Smoked - listed only)
- Disease characteristics (listed only):
- Tumor type
- For Melanoma: stage and disease classification at initial diagnosis; stage and disease classification at study entry
- For NSCLC: stage, disease classification and cell type at initial diagnosis; stage and disease classification at study entry
- For RCC: stage and cell type at initial diagnosis; stage and disease classification at study entry
- For Bladder Cancer: stage, disease classification, location and minor histological variants at initial diagnosis; stage, disease classification and location at study entry
- For CRC: stage, disease classification, cell type and location at initial diagnosis; stage and disease classification at study entry
- For SCLC: stage and cell type at initial diagnosis; stage and disease classification at study entry
- For Breast Cancer: stage, disease classification and cell type at initial diagnosis; stage and disease classification at study entry
- For Pancreatic Cancer: stage and cell type at initial diagnosis; stage and disease classification at study entry

- For Hepatocellular Carcinoma: stage and cell type at initial diagnosis; stage at study entry
- For Head and Neck: stage, cell type and location at initial diagnosis; stage at study entry
- For Gastric Cancer: stage at initial diagnosis; disease classification and cell type at study entry
- For Esophageal Cancer: stage at initial diagnosis; disease classification, cell type and location at study entry
- For Gastroesophageal Junction: stage at initial diagnosis; disease classification and cell type at study entry
- For Other Solid Tumors: stage and cell type at initial diagnosis; stage and disease classification at study entry

7.3.3 Medical History

A by-subject listing of general medical history for all treated subjects will be provided.

7.3.4 Prior Therapy Agents

Prior systemic cancer therapy (regimen setting, number of regimen, line of therapy, best response to latest regimen etc.) will be summarized and listed by subject.

Prior radiotherapy (Yes/No) and prior surgery (Yes/No) will be summarized and listed by subject.

7.3.5 Physical Examinations

Subjects with abnormal baseline physical examination will be listed by subject.

7.3.6 Baseline Physical Measurements

Baseline physical measurements will be listed by subject.

7.4 Extent of Exposure

Listings will include all available exposure data. Analyses will be performed on all treated subjects, unless otherwise specified.

The treatment period consists of two phases:

- 2 weeks of monotherapy lead-in (Cycle 0) during which single oral daily dose of BMS-986205 monotherapy is administered daily, and
- 48 weeks of combination therapy whereby each treatment cycle is 4 weeks and is comprised of daily doses of BMS-986205 and 1 dose of nivolumab administered every 4 weeks on Day 1 of the treatment cycle up to 12 cycles.

All participants completing approximately 48 weeks of combination study therapy with ongoing disease control (CR, PR, or SD) may be eligible for an additional 48 weeks of study therapy at the originally assigned dose regimen beyond the initial 48 weeks.

The cycle start date will correspond to the dosing date. Extent of Exposure will be assessed separately for the 2-week lead in period for mono BMS-986205 and the drugs in combination.

7.4.1 Administration of Study Therapy

The following parameters will be summarized (descriptive statistics) by phase and study therapy:

- Number of doses received
- Cumulative dose (mg) = the sum of all actual doses that a subject received
- Duration of study therapy (weeks)
- Dose intensity (mg/weeks) = cumulative dose (mg) / duration of therapy (weeks)
- Relative dose intensity (%)
- Relative dose intensity (%) using the following categories: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%

Exposure parameter derivation for each treatment are shown in Table 7.4.1-1.

Table 7.4.1-1: Administration of study therapy: definition of parameters

Parameter	BMS-986205	Nivolumab
Dosing schedule per protocol	100 mg QD	480 mg Q4W
Cumulative Dose (mg)	Cum dose (mg) is sum of the doses (mg) administered to a subject during the treatment period.	
Duration of study therapy (week)	(Last dose date - Start dose date + 1) / 7	(Last dose date - Start dose date + 28) / 7
Dose intensity (mg/week)	Cum dose (mg) / Duration of Therapy (week)	
Relative dose intensity (%)	[Dose Intensity / (100 × 7)] × 100	[Dose Intensity /(480 / 4)] × 100

A by-subject listing of dosing of study medications (record of study medication, infusion details, and dose changes) and a by-subject listing of exposure parameters (number of doses, duration of therapy, cumulative dose, dose intensity, and relative dose intensity) will be also provided.

7.4.2 Modifications of Study Therapy

7.4.2.1 Dose Delays

Each BMS-986205 and nivolumab may be delayed.

A dose of nivolumab 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 nivolumabIDO1 inhibitor.

BMS-986205 is administered as a tablet daily. A dose of BMS-986205 will be considered as actually delayed (interrupted) if BMS-986205 was not administrated for at least 1 day. Interruption means the continuous oral dosing was stopped or held for a period of time prior to resuming.

All study drugs must be delayed until treatment can resume. Reason for dose delay will be retrieved from CRF dosing pages.

The following parameters will be summarized by study drug:

- Number of subjects with at least one dose delayed, the number of dose delays per subject, the reason for dose delay and the length of dose delay.

7.4.2.2 Infusion Interruptions and Rate Changes

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

The following parameters will be summarized:

- 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, the reason for reduction and the number of infusion with IV rate reduction per subject.

7.4.2.3 Dose Escalations

Dose escalations (within subject) are not permitted for nivolumab.

7.4.2.4 Dose Reductions

Dose reductions (within subject) are not permitted for nivolumabIDO1 inhibitor.

Number of subjects with at least one dose reduction, the reason for dose reduction, and the number of dose reductions per subject will be summarized for BMS-986205 only.

7.4.2.5 Dose Discontinued

Number of subjects with dose discontinued along with the reason will be summarized by study drug.

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 UMC WHO Drug Global Dictionary.

A by-subject listing of concomitant medications will be provided..

Prior medications, defined as non-study medications with a start date before consent date, and current medications, defined as non-study medications with a start date before the first date of study medication and stop date after consent date, will be coded using the UMC WHO Drug Global Dictionary.

A by-subject listing of prior/current medications will be provided..

7.4.3.1 Immune modulating medication

Immune modulating concomitant medications are medications entered on an immune modulating medication form or available from the most current pre-defined list of immune modulating medications. The list of anatomic class, therapeutic class and generic name used for the selection at the time of the database lock will be provided.

A by-subject listing of concomitant immune modulating medications will be provided.

7.4.3.2 Subsequent Cancer Therapy

A by-subject listing of subsequent cancer therapy (systemic anti-cancer therapy, radiotherapy and surgery) will be produced for all treated subjects.

7.5 Efficacy

Analyses in this section will be tabulated for all treated subjects, unless otherwise specified.

7.5.1 Analysis of Objective Response Rate

One of the objectives of the study is to estimate the ORR per investigator among all treated subjects. ORR with corresponding 2-sided 95% CI based on the Clopper and Pearson[4] method will be presented.

The number and percentage of subjects in each category of BOR per investigator (complete response [CR], partial response [PR], stable disease [SD], progressive disease [PD], or unable to determine [UTD]) will be presented. Estimates of response rate, along with its exact two-sided 95% CI by Clopper and Pearson[5] will be presented.

A by-subject listing of best overall response will be presented including best overall response per investigator and dates of CR/PR/progression.

A by-subject listing of lesion evaluations per investigator will be presented.

A by-subject listing of per time point tumor response per investigator will be also presented.

7.5.2 Duration of Response

Duration of response (DOR) will also be evaluated for subjects who achieved confirmed PR or CR. The DOR will be estimated using the Kaplan-Meier (KM) product limit method and will be displayed graphically. A table will be produced presenting number of events, number of subjects involved, medians, and 95% CIs for the medians. Median values of DOR, along with two-sided 95% CI will be computed based on a log-log transformation method.

A by-subject listing will be presented including best response, duration of response, whether the subject was censored for duration of response, and, if so, the reason.

7.6 Safety

Analyses in this section will be tabulated for all treated subjects by phase (monotherapy lead-in, combination) and overall, unless otherwise specified.

7.6.1 Deaths

Deaths will be summarized:

- All deaths, reasons for death.
- Deaths within 100 days of last dose received, reasons for death.

A by-subject listing of deaths will be provided for the all enrolled subjects population.

7.6.2 Serious Adverse Events

Serious adverse events will be summarized :

- Overall summary of SAEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.
- Overall summary of drug-related SAEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.

A by-subject SAE listing will be provided for the "enrolled subjects" population.

7.6.3 Adverse Events Leading to Discontinuation of Study Therapy

AEs leading to discontinuation will be summarized:

- Overall summary of AEs leading to discontinuation by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.
- Overall summary of drug-related AEs leading to discontinuation by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.

A by-subject AEs leading to discontinuation listing will be provided.

7.6.4 Adverse Events Leading to Dose Modification

AEs leading to dose delay/reduction will be summarized:

- Overall summary of AEs leading to dose delay/reduction by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.
- Overall summary of related AEs leading to dose delay/reduction by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.

A by-subject AEs leading to dose delay/reduction listing will be provided.

7.6.5 Adverse Events

Adverse events will be summarized:

- Overall summary of any AEs by worst CTC grade (1, 2, 3, 4, 5, not reported, total) presented by SOC/PT.

- Overall summary of any AEs that required immune modulating medication by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.
- Overall summary of drug-related AEs by worst CTC grade (1, 2, 3, 4, 5, not reported, total) presented by SOC/PT.
- Overall summary of drug-related AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.

A by-subject AE listing will be provided. A by-subject listing of any AE requiring immune modulating medications will also be provided.

7.6.6 Select Adverse Events (EU/ROW Submissions)

Unless otherwise specified, analyses will be performed by select AE category. Analyses will also be repeated by subcategory of endocrine events.

7.6.6.1 Incidence of Select AE

Select AEs will be summarized for each category/subcategory:

- Overall summaries of any select AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category or Subcategory/PT.
- Overall summaries of any drug-related select AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category or Subcategory/PT.
- Overall summaries of any serious select AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category or Subcategory /PT.
- Overall summaries of drug-related serious select AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category or Subcategory /PT.
- Overall summaries of any select AEs leading to discontinuation by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category or Subcategory /PT.
- Overall summaries of drug-related select AEs leading to discontinuation by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category or Subcategory /PT.
- Summary of frequency of unique select AEs by Category.

A by-subject select AE listing will be provided.

7.6.7 Immune-Mediated Adverse Events (US Submission)

A by-subject listing of IMAEs will be provided. For new studies which collect investigator assessment of potential IMAE data, a by-subject listing of AEs considered as immune-mediated events per investigator but not qualified for IMAEs definition will also be provided.

[redacted]

[redacted]

7.6.9 Multiple Events

A listing displaying the unique instances of all AEs, i.e., after duplicates have been eliminated and overlapping and contiguous occurrences of the same event (i.e. same PT) have been collapsed will be provided.

7.6.10 Laboratory Parameters

The analysis population for each laboratory test is restricted to treated subjects who underwent that laboratory test. Laboratory tests (in addition to the tests specified below) with CTC criteria collected in the specific studies may also be included in the summaries.

7.6.10.1 Hematology

The following will be summarized as worst CTC grade on-treatment per subject and as shift table of worst on-treatment CTC grade compared to baseline CTC grade per subject: hemoglobin (HB), platelets, white blood counts (WBC), absolute neutrophils count (ANC) and lymphocyte count (LYMPH).

A by-subject listing of these laboratory parameters will be provided.

7.6.10.2 Serum Chemistry

The following will be summarized as worst CTC grade on-treatment per subject and as shift table of worst on-treatment CTC grade compared to baseline CTC grade per subject: ALT, AST, alkaline phosphatase (ALP), total bilirubin and creatinine.

A by-subject listing of these laboratory parameters will be provided.

7.6.10.3 Electrolytes

The following will be summarized as worst CTC grade on-treatment per subject and as shift table of worst on-treatment CTC grade compared to baseline CTC grade per subject: sodium (high and low), potassium (high and low), calcium (high and low), magnesium (high and low), and Glucose Serum (fasting hyperglycemia and hypoglycemia regardless of fasting status).

A by-subject listing of these laboratory parameters will be provided.

7.6.10.4 Methemoglobin

The number of subjects with highest methemoglobin post baseline >10% will be summarized.

A by-subject listing of these subjects will be provided.

7.6.10.5 Additional Analyses

In addition, further analyses on specific laboratory parameters will be performed:

Abnormal Hepatic Function Test

The number of subjects with the following laboratory abnormalities from on-treatment evaluations will be summarized:

- ALT or AST > 3 x ULN, > 5 x ULN, > 10 x ULN and > 20 x ULN
- Total bilirubin > 1.5 x ULN and > 2 x ULN
- Concurrent (within 1 day) ALT or AST > 3 x ULN and total bilirubin > 2 x ULN
- Concurrent (within 30 days) ALT or AST > 3 x ULN and total bilirubin > 2 x ULN

A by-subject listing of these specific abnormalities will be provided.

Abnormal Thyroid Function Test

The number of subjects with the following laboratory abnormalities from on-treatment evaluations will be summarized:

- TSH value > ULN and
  - with baseline TSH value ≤ ULN
  - with at least one FT3/FT4 test value < LLN within 2-week window after the abnormal TSH test
  - with all FT3/FT4 test values ≥ LLN within 2-week window after the abnormal TSH test
  - with FT3/FT4 missing within 2-week window after the abnormal TSH test
- TSH < LLN and
  - with baseline TSH value ≥ LLN
  - with at least one FT3/FT4 test value > ULN within 2-week window after the abnormal TSH test
  - with all FT3/FT4 test values ≤ ULN within 2-week window after the abnormal TSH test
  - with FT3/FT4 missing within 2-week window after the abnormal TSH test

A by-subject listing of these specific abnormalities will be provided.

7.6.11 Vital Signs and Pulse Oximetry

Vital signs will be summarized by timepoint.

Vital signs and pulse oximetry (i.e. % oxygen saturation) collected on the CRF will be provided in separate listings.

7.6.12 Electrocardiograms

All of the available ECG parameter values from each subject will be included in the ECG data set.

Baseline values are defined as the last recorded values prior to the first dosing. For ECG parameters such as heart rate (HR), QT, QRS, QTcB, QTcF and PR, summary measures (n, mean, standard deviation, median, minimum, and maximum) will be provided.

A by-subject listing of all ECG measures and a listing of abnormal ECG interpretations will be provided.

7.6.13 Physical Measurements

Physical measurements will be listed by subject.

7.6.14 Immunogenicity Analysis

Further details on immunogenicity [redacted] definitions, population for analyses and endpoints are described in APPENDIX 2.

Incidence of ADA

Number (%) of subjects will be reported for the following parameters based on Evaluable Subjects.

- Baseline ADA-positive
- ADA-positive
  - Persistent Positive (PP)
  - Not PP-Last Sample Positive
  - Other positive
  - Neutralizing Positive
- ADA-negative

A listing of all ADA assessments will be provided. A separate listing of ADA assessments of nivolumab for subjects with neutralizing positive will also be provided.

Clinical implications

Clinical implications of nivolumab immunogenicity will be primarily focused on subjects with persistent ADA-positive relative to ADA-negative. Subjects with any ADA-positive samples after initiation of treatment (relative to baseline) may be used to explore clinical implications. Effect of immunogenicity on safety will be explored by examining the type of AEs [redacted] such as hypersensitivity/infusion reaction. Individual subject's safety profile will be examined and described based on a listing. Clinical implications on efficacy will also be explored similarly. Association between trough concentrations of nivolumab and ADA assessments may be explored, as needed.

7.6.15 Pregnancy

A by-subject listing of pregnancy tests results will be provided for treated female subjects.

7.7 Pharmacokinetics

The BMS-986205 and nivolumab concentration data obtained in this study will also be combined with data from other studies in the clinical development program to develop a population PK

model. This model will be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of BMS-986205 and nivolumabIDO1 inhibitor. In addition, exposure-response analyses with selected efficacy and safety endpoints may be conducted. Results of population PK and exposure response-analyses will be reported separately.

7.7.1 Pharmacokinetic Concentrations

Analyses for this section will be provided by the CPAR group. Summary statistics and listings will be provided for the following pharmacokinetic concentrations by treatment, cycle, study day and time on the BMS-986205 and nivolumab PK Subjects.

- Plasma concentrations of BMS-986205 and select metabolites
- Serum concentrations of nivolumab

Plots of the individual and mean concentration profile vs. time by cycle/study day for BMS-986205 and select metabolites will be provided.

A by-subject listing of BMS-986205/select metabolites plasma and nivolumab serum concentrations will be provided.

7.7.2 Pharmacokinetic Parameters

Summary statistics will be provided for all individual PK parameters by treatment, cycle, study day and time where data is available. Geometric means and coefficients of variation will be presented for the selected following PK parameters for BMS-986205 or corresponding metabolites: Cmax, AUC(TAU), CLT/F, Ctrough, AI, %UR24, MR_AUC(TAU) and MR_Cmax. Mean and standard deviation will be presented for T-HALF(T-HALFeff_AUC). Median, minimum, and maximum will be presented for Tmax. Drug accumulation indices (AI) is defined as the ratio of AUC(TAU) and Cmax at steady state to after the first dose. Effective T-Half, which will be caluclated only if AI >1, is defined as following:

$$\text{Effective T} - \text{Half} = \frac{dosing\ interval * \ log(2)}{log(\frac{AI}{AI-1})}$$

Plot of geometric mean with 90% CI of Ctrough vs. study day and cycle will be presented to assess if steady state is reached.

Summary statistics will be provided for the following PK parameters for nivolumab: Ctrough, Ceoi.

A by-subject listing of BMS-986205/select metabolites and nivolumab PK parameters will be provided.

7.7.3 PK Analysis of Urinary recovery data

Urinary recovery data of BMS-986205/select metabolites will be listed if available.

7.8 Pharmacodynamics

Summary statistics of change from baseline for serum kynurenine and tryptophan and corresponding percent change from baseline (C1D1) will be summarized by timepoint.

Line graphs summarizing the mean of absolute and relative (change from baseline and percent change from baseline) values by timepoint will be produced.

8 CONVENTIONS

8.1 General

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

- For missing and partial adverse event onset dates, imputation will be performed using the Adverse Event Domain Requirements Specification[6]
- For missing and partial adverse event resolution dates, imputation will be performed as follows (these conventions may change):
  - If only the day of the month is missing, the last day of the month will be used to replace the missing day. If the imputed date is after the death date or the last known alive date, then the latest known alive date or death date is considered as the resolution date.
  - If the day and month are missing or a date is completely missing, it will be considered as missing.
- Missing and partial non-study medication domain dates will be imputed using the derivation algorithm described in 4.1.3 of BMS Non-Study Medication Domain Requirements Specification[7].
- Missing and partial radiotherapy and surgery dates will be imputed using algorithm described in APPENDIX 1.
- For death dates, the following conventions will be used for imputing partial dates:
  - If only the day of the month is missing, the 1st of the month will be used to replace the missing day. The imputed date will be compared to the last known alive date and the maximum will be considered as the death date.
  - If the month or the year is missing, the death date will be imputed as the last known alive date.
  - If the date is completely missing but the reason for death is present, the death date will be imputed as the last known date alive.
- For other partial/missing dates, the following conventions were used:
  - If only the day of the month is missing, the 15th of the month will be used to replace the missing day.
  - If both the day and the month are missing, “July 1” will be used to replace the missing information.
  - If a date is completely missing, it will be considered as missing.

The following conversion factors will be used to convert days to months or years:

1 month = 30.4375 days and 1 year = 365.25 days.

Duration (e.g. time-to onset, time-to resolution) will be calculated as follows:

Duration = (Last date - first date + 1)

Last known alive date will be defined based on all appropriate dates collected on the CRF.

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

8.2 Pharmacokinetic Summaries

In-text Tables

For in-text pharmacokinetic tables, coefficient of variation (%CV) will be reported as integers. For other statistics except for standard deviations, values of 100 or higher will be presented as integers, values of 10 - < 100 will be displayed to one decimal place, and values of 1 - < 10 will be displayed to two decimal places. Values less than 1 will be displayed to three decimal places. Ratios will also be displayed to three decimal places. Standard deviations will be reported to a precision of 1 decimal place more than the mean.

Handling of Non-Quantifiable Concentrations

For the summaries of PK concentration-time data, concentrations that are less than the lower limit of quantification (LLOQ) should be displayed as "< LLOQ" in the listings and be treated as missing in summary tables and plots. For the purpose of calculating PK parameters, other than Ctrough, pre-dose concentrations that are less than LLOQ and concentrations prior to the first quantifiable concentration that are less than LLOQ will be set to zero, and all other concentrations less than LLOQ will be set to missing. Summary statistics for Ctrough concentrations will be calculated by imputing values less than LLOQ as ½ * LLOQ.

All available PK concentration-time data and derived pharmacokinetic parameter values will be included in the PK data set and listed accordingly.

Treatment of Outliers

Individual PK concentrations, if deemed to be anomalous, may be excluded from the analysis following a review of available documentation (e.g., bioanalytical report, clinical data). Any such exclusion will be clearly listed in the study report along with justification for exclusion.

Entire PK concentration-time profiles for a subject may be excluded following review of available documentation (e.g., bioanalytical report, clinical data). However, results of analysis with and without the excluded profiles may be presented in the study report. Any such exclusion will be clearly listed in the study report along with justification for exclusion.

PK Exclusions

PK Analysis, Reporting, and Exclusion criteria should follow the BMS PK Harmonization document Version 4.0.

9 CONTENT OF REPORTS

The complete list of analyses contributing to the clinical study report and other possible analyses will be given in the Data Presentation Plan.

10 DOCUMENT HISTORY

Table 10-1: Document History

Version Number	Author(s)	Description
1.0	[redacted]	Original Issue

APPENDIX 1 MISSING AND PARTIAL RADIOTHERAPY AND SURGERY DATES IMPUTATION ALGORITHMS

Procedures – Imputation Rules.

If reported procedure start date is a full valid date then set start date equal to the date part of procedure start date.

In case of partial date use imputation rules described below:

- If only day is missing then
  - If month and year of procedure match month and year of first dose date then impute as date of first dose;
  - If month and year of procedure don't match month and year of first dose date then impute as first day of that month and year.
- If both day and month are missing, then impute as maximum between 01JAN of the year and date of the first dose;
- If date is completely missing or invalid then leave missing.

Note: Imputation is not applicable to data where start date is not collected (for example "PRIOR RADIOTHERAPY" CRF). Set start date to missing in this case.

If reported end date is a full valid date then set end date equal to the date part of the reported end date.

In case of partial date use imputation rules described below:

- If reported end date is partial then set end date equal to the last possible reported end date based on the partial entered reported end date.
- If reported end date is missing, continuing, unknown or invalid then set end date equal to the most recent database extraction date.

If end date was imputed then compare end date to the death date or last known alive date if subject is not dead. If posterior then end date should be imputed to death date (or last known alive date if subject not dead).

Note: Imputation of partial dates only applies to data entered on "RADIOTHERAPY" CRF page. For other CRF pages in case of partial dates set end date to missing.

Surgeries – Imputation Rules.

If reported surgery date is a full valid date then set start date equal to the date part of surgery date.

In case of partial date, use one of the two imputation rules described below:

A. For data collected on "PRIOR SURGERY RELATED TO CANCER" CRF page:

- If only day is missing then impute as the first day of the month;

- If both day and month are missing then then impute as 01JAN of the year;
- If date is completely missing or invalid then leave missing.

B. For data collected on other CRF pages (deemed to be on-treatment/subsequent surgeries):

- If only day is missing then
  - If month and year of surgery match month and year of first dose date then impute the missing date as the date of first dose;
  - If month and year of surgery don't match month and year of first dose date then impute as first day of that month and year;
- If both day and month are missing then impute as maximum between 01JAN of the year and date of the first dose;
- If date is completely missing or invalid then leave missing.

APPENDIX 2 IMMUNOGENICITY ANALYSIS [redacted]

[redacted]

Immunogenicity Endpoints

A fundamental metric that informs clinical immunogenicity interpretation is the incidence of ADA in a study or across comparable studies. ADA incidence is defined as the proportion of the study population found to have seroconverted or boosted their pre-existing ADA during the study period.

Terms and Definitions

Validated ADA test methods enable characterization of samples into ADA-positive vs. ADA-negative. To classify the ADA status of a subject using data from an in vitro test method, each sample from the subject is categorized based on the following definitions:

Sample ADA Status**:**

- Baseline ADA-positive sample: ADA is detected in the last sample before initiation of treatment
- Baseline ADA-negative sample: ADA is not detected in the last sample before initiation of treatment
- ADA-positive sample: After initiation of treatment, (1) an ADA detected (positive seroconversion) sample in a subject for whom ADA is not detected at baseline, or (2) an ADA detected sample with ADA titer to be at least 4-fold or greater (≥) than baseline positive titer
- ADA-negative sample: After initiation of treatment, ADA not positive sample relative to baseline

Next, using the sample ADA status, subject ADA status is defined as follows:

Subject ADA Status:

- Baseline ADA-positive subject: A subject with baseline ADA-positive sample
- **ADA-positive subject**: A subject with at least one ADA positive-sample relative to baseline at any time after initiation of treatment

1) *Persistent Positive (PP):* ADA-positive sample at 2 or more consecutive time points, where the first and last ADA-positive samples are at least 16 weeks apart
2) *Not PP-Last Sample Positive:* Not persistent positive with ADA-positive sample at the last sampling time point

3) *Other Positive:* Not persistent positive but some ADA-positive samples with the last sample being negative
4) *Neutralizing Positive:* At least one ADA-positive sample with neutralizing antibodies detected

- **ADA-negative subject:** A subject with no ADA-positive sample after the initiation of treatment.

(Note: 16 weeks was chosen based on a long half-life of IgG4.)

Population for Analyses

Analysis of immunogenicity data will be based on ADA evaluable subjects defined as all treated subjects with baseline and at least 1 post-baseline immunogenicity assessment. Analysis dataset and data listing will include all available ADA samples. However, subject-level ADA status will be defined based on only adequate samples (e.g., excluding 1-hour post-infusion samples when clearly indicated).