Official Title of Study:

A Phase 1 Study of Cabiralizumab (BMS-986227, FPA008) Administered Alone or in Combination with Nivolumab (BMS-936558) in Advanced Malignancies

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STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

A PHASE 1 STUDY OF CABIRALIZUMAB (BMS-986227, FPA008) ADMINISTERED ALONE OR IN COMBINATION WITH NIVOLUMAB (BMS-936558) IN ADVANCED MALIGNANCIES

PROTOCOL(S) CA025001

VERSION # 3.0

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2 STUDY DESCRIPTION

2.1 Study Design

This study is a Phase 1, open-label, dose escalation study to evaluate the safety, tolerability, PK, and PD and preliminary anti-tumor activity of cabiralizumab as monotherapy in subjects with advanced solid tumor. In addition, the study will evaluate the safety profile, PK, PD and preliminary anti-tumor activity of cabiralizumab in combination with nivolumab in subjects with advanced solid tumors and hematologic malignancies.

For the monotherapy cohorts of the study, cabiralizumab will be given on Day 1 of each 14-day treatment cycle until the progression of disease, discontinuation due to toxicity, withdrawal of consent or study closure. For the combination cohorts of the study, cabiralizumab and nivolumab will be given on Day 1 of each 14-day treatment cycle until the progression of disease, discontinuation due to toxicity, withdrawal of consent or study closure. Nivolumab will be administered as an IV infusion over 30 minutes, and then cabiralizumab will be administered as an IV infusion over 30 minutes.

This study consists of 2 planned cabiralizumab monotherapy cohorts (M1: 2 mg/kg and M2: 4 mg/kg) and 2 cohorts of cabiralizumab in combination with nivolumab (C1: 4 mg/kg cabiralizumab and 3 mg/kg nivolumab in subjects with solid tumors and C2: 4 mg/kg cabiralizumab and 3 mg/kg nivolumab in subjects with hematologic malignancies).

The study will consist of 3 periods: Screening, Treatment and Follow-up. The study will end after the last subject completes the last visit.

Screening begins by establishing the subject's initial eligibility and signing of the informed consent form (ICF). Subjects must have treatment assignment within 28 days after signing the informed consent.

The Treatment Phase begins when the treatment cohort is assigned to the subjects. The subject will be assigned to the open cohort (M1, M2, C1, or C2) at the timing of the treatment assignment. First dose should be started within 3 days of treatment assignment. The subjects will be required to be hospitalized for safety evaluation at least for 8 days from the first dose. The subjects can be discharged at the investigator's discretion at Day 8.

The Follow-Up Phase begins when the decision to discontinue a subject from all treatment is made. Subjects will be followed for drug-related toxicities until these toxicities resolve, return to baseline, or are deemed irreversible. All adverse events will be documented for a minimum of 100 days after the last dose of study medication. The study design schematic is presented in Figure 2.1-1 and Figure 2.1-2.

Figure 2.1-1: Dose Escalation Schematic

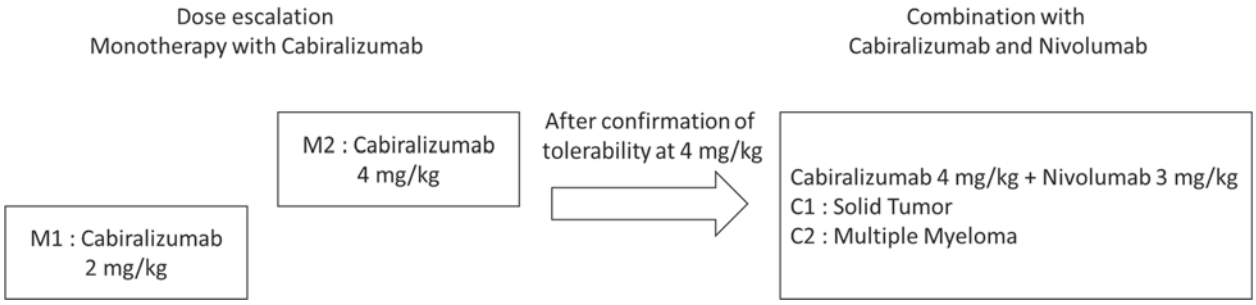
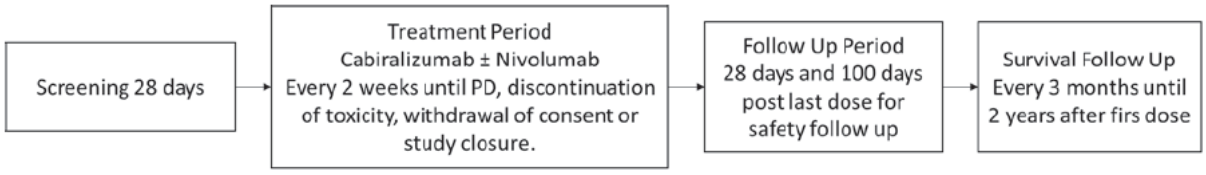


Figure 2.1-2: Study Design Schematic



2.2 Treatment Assignment

The selection and timing of dose for each participant is as follows:

Table 2.2-1: Selection and Timing of Dose

Cohort	Study Treatment	Unit dose strength(s)/Dosage level(s)	Dosage formulation Frequency of Administration	Route of Administration
M1*	Cabiralizumab	2 mg/kg	Every 2 weeks	Intravenous
M2	Cabiralizumab	4 mg/kg	Every 2 weeks	Intravenous

Table 2.2-1: Selection and Timing of Dose

Cohort	Study Treatment	Unit dose strength(s)/Dosage level(s)	Dosage formulation Frequency of Administration	Route of Administration
C1/C2	Cabiralizumab	4 mg/kg	Every 2 weeks	Intravenous
	Nivolumab	3 mg/kg	Every 2 weeks	Intravenous

*: A lower dose may be tested if appropriate.

Sponsor has the option to expand combination cohorts (up to 12 subjects in total per each combination cohort) at the dose previously established to be safe in order to obtain additional data or to investigate alternative dose levels to those defined in the protocol.

No within-subject dose escalations will be permitted. If a dose level is found to exceed the MTD subjects enrolled in that dose level may be treated at a lower dose following consultation and agreement between Investigators, the Sponsor and Efficacy and Safety Review Committee.

2.3 Blinding and Unblinding

Not Applicable.

2.4 Protocol Amendments

This SAP incorporates the following revised protocols.

Table 2.4-1: Revised Protocols

No	Date of Issue	Summary of Major Changes
Original	17-Jan-2017	
Revised 01	08-Mar-2017	Added clarification of DLT evaluable participants etc.
Revised 02	06-Jul-2017	Added clarification of the allowance on treatment phase procedural outline etc.
Revised 03	12-Sep-2017	DLT criteria incorporated with other ongoing studies.
Revised 04	17-Oct-2017	Removed Survival follow up after Follow up Period.
Revised 05	22-Mar-2018	Added Clarification in bone marrow sample for efficacy assessments in subjects with Multiple Myeloma

3 OBJECTIVES

3.1 Primary

- To assess the safety and tolerability of cabiralizumab as monotherapy in subjects with advanced solid tumors.

3.2 Secondary

- To assess the safety of cabiralizumab in combination with nivolumab in subjects with advanced solid tumors and hematologic malignancies.
- To characterize the PK profile of cabiralizumab administered alone and in combination with nivolumab.
- To characterize the immunogenicity of cabiralizumab and nivolumab
- To assess the preliminary anti-tumor activity of cabiralizumab administered alone and in combination with nivolumab in subjects with advanced solid tumors.
- To assess the preliminary anti-tumor activity of cabiralizumab administered in combination with nivolumab in subjects with hematologic malignancies.

[redacted]

4 ENDPOINTS

4.1 Primary Endpoints

The assessment of safety of cabiralizumab as monotherapy 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, other events of interest (OEOI), and deaths. In addition clinical laboratory tests, and immunogenicity (i.e. development of anti-drug antibody) will be analyzed.

4.2 Secondary Endpoints

4.2.1 Safety of Cabiralizumab in Combination with Nivolumab

Same as Section 4.1.

4.2.2 Preliminary Antitumor Activity in Subjects with Advanced Solid Tumors

The following set of study-level efficacy endpoints will be used for comprehensive assessment of antitumor activity.

4.2.2.1 Objective Response Rate

Objective Response Rate (ORR) is defined as the number of treated subjects who achieve a best response of complete response (CR) or 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 treatment and the date of objectively documented progression per RECIST v1.1 criteria or the date of subsequent therapy, whichever occurs first. For subjects without documented

progression or subsequent therapy, all available response designations will contribute to the BOR determination. Confirmation of response is required at least 4 weeks after the initial response.

4.2.2.2 Duration of Response

Duration of Response (DOR) is defined as the time between the date of first 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.

4.2.3 Preliminary Antitumor Activity in Subjects with Hematologic Malignancies

The following set of study-level efficacy endpoints will be used for comprehensive assessment of antitumor activity.

4.2.3.1 Objective Response Rate

Objective Response Rate (ORR) is defined as the number of treated subjects who achieve a best response of stringent complete response (sCR), complete response (CR), very good partial response (VGPR) or partial response (PR) based on investigator assessments (using IMWG Response criteria) divided by the number of all treated subjects.

4.2.3.2 Duration of Response

Duration of Response (DOR) is defined as the time between the date of first documented response (sCR, CR, VGPR or PR) to the date of the first documented tumor progression as determined by the investigator (per IMWG Response 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 sCR, CR, VGPR or PR) only.

4.3 Other Endpoints

4.3.1 Pharmacokinetics

PK will be determined from serum nivolumab concentrations. Samples will be collected to characterize pharmacokinetics of nivolumab and to explore exposure-safety and exposure-efficacy relationships.

The PK of BMS-986227 will be derived from serum concentration versus time data. The PK parameters that will be assessed, following the intensive PK collection, are shown in Table 4.3.1-1.

Table 4.3.1-1: Pharmacokinetic Parameters

Parameters	Definition
Cmax	Maximum observed serum concentration
Tmax	Time of maximum observed serum concentration
AUC(0-t)	Area under the serum concentration-time curve from time zero to time of last quantifiable concentration after the first dose
AUC(TAU)	Area under the serum concentration-time curve in one dosing interval
AI_Ctrough	Ctrough Accumulation Index; ratio of Ctrough at steady-state (i.e. Cycle 8) to Ctrough after the first dose
T-HALFeff_Ctrough	Effective elimination half-life that explains the degree of Ctrough accumulation observed
Parameter to be reported as a separate listing and summary	
Ctrough	Trough observed serum concentration (predose at each cycle)

See Section 7.7.4 for the detail of Ctrough Accumulation Index and Effective elimination half-life.

PK of nivolumab will be determined from serum nivolumab concentrations. Trough observed serum concentrations and concentrations for end of infusion samples will be summarized and listed. Pharmacokinetics of BMS-986227 and nivolumab will also be used to explore PK-biomarker, exposure-safety and exposure-efficacy relationships.

[redacted]

[redacted]

4.3.3 Immunogenicity

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.

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

Table 4.3.3-1: Sample ADA Status

Sample ADA Status	Definition
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	1) an ADA detected (positive seroconversion) sample in a participant 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, participant ADA status is defined as follows:

Table 4.3.3-2: Participant ADA Status

ADA Status	Definition
Baseline ADA-positive	A participant with baseline ADA-positive sample
ADA-positive	A participant with at least one ADA positive-sample relative to baseline at any time after initiation of treatment
• Persistent Positive (PP)	ADA-positive sample at 2 or more consecutive timepoints, where the first and last ADA-positive samples are at least 16 weeks apart
• Not PP-Last Sample Positive	Not persistent positive with ADA-positive sample at the last sampling timepoint
• Other Positive	Not persistent positive with ADA-negative sample at the last sampling timepoint
ADA-negative	A participant with no ADA-positive sample after the initiation of treatment

They are applicable for both Cabiralizumab and Nivolumab.

5 SAMPLE SIZE AND POWER

This is a Phase 1 safety study and the sample size cannot be precisely determined and depends on the observed toxicities. Between 6 and 12 participants are expected to be treated during dose escalation (Part 1), assuming 2 mg/kg and 4 mg/kg cabiralizumab monotherapy are explored. On the combination cohorts, 6 subjects each cohort are expected to be treated with 4 mg/kg cabiralizumab in combination with 3 mg/kg nivolumab following the dose escalation part of monotherapy. In addition, Sponsor has the option to expand combination cohorts (up to 12 subjects in total per each combination cohort) at the dose previously established to be safe in order to obtain additional data or to investigate alternative dose levels to those defined in the protocol.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

- Baseline period:
  - Baseline evaluations or 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 and 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 and vital signs) will be defined as evaluations with a date on or prior to the day of first dose of study treatment.
  - If there are multiple valid assessments on or prior to the first dose of study treatment:
    - For laboratory tests, the latest non missing labs value on or before first dose date (and time if collected) will be used as the baseline in the analyses. For 'LIPASE' and 'GLUCOSE', for treated subjects only, the last predose assessment with non-missing toxicity grade will be considered as baseline. If multiple assessments exist with the same collection date (and time if collected) and entry date and time, then the first observation is used as baseline.
    - For Eastern Cooperative Oncology Group (ECOG) performance status (PS), the latest ECOG PS value prior to or on the first dose date (and time if collected) will be used as the baseline in the analyses. If multiple records fall on the last date then the record with the highest value of ECOG PS will be considered as baseline.
    - For Anti-Drug Antibody (ADA), the record related to the most recent assessment among those records where date (and time if collected) of Cabiralizumab or Nivolumab immunoglobulin (IMG) assessment is less than or equal to the date (and time if collected) of the first Cabiralizumab or Nivolumab dose date.

- 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 30 days (or 100 days depending on the analysis) after the last dose of 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.
  - 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 30 days (or 100 days depending on the analysis) after the last dose of study treatment.

6.2 Treatment Regimens

Unless otherwise specified, the safety and efficacy analysis will be based on the treatment group "as treated".

6.3 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign informed consent
Treated	All participants who take any dose of study treatment.
Pharmacokinetic	All treated participants who have evaluable concentration-time data
Immunogenicity	All treated participants who have baseline and at least one post baseline pre-infusion immunogenicity assessment
[redacted]	[redacted]

7 STATISTICAL ANALYSES

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%. Continuous variables will be summarized by cohort using the mean, standard deviation, median, minimum, and maximum values.

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, and Serious 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 was discontinued".

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

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 events results will be graded for severity using NCI Common Terminology Criteria for Adverse Events (CTCAE) and the most recent version of the criteria at the time of the database lock 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 of the experimental arm when arms are presented side-by-side.

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

7.1.1.1 Other Events of Interest

Other events of interest (OEOI) consist of a list of preferred terms grouped by specific category (e.g. Periorbital Edema, AST Abnormality, ALT Abnormality, CK Abnormality, Myositis Event, Myocarditis Event, Demyelination Event, Guillain-Barre Syndrome, Pancreatitis Event, Uveitis Event, Encephalitis Event, Myasthenic Syndrome, Rhabdomyolysis Event, Graft Versus Host Disease). The list of MedDRA preferred terms used to identify OEOI 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 analyzed using International System of Units (SI).

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 immunogenicity analysis will be collected from subjects according to the protocol schedule. Samples will be evaluated for development of Anti-Drug Antibody (ADA).

7.2 Study Conduct

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 enrolled subjects by cohort, unless otherwise specified.

7.3.1 Subject Disposition

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

Number of subjects who discontinued study treatment along with corresponding reason will be tabulated by cohort. Reason for discontinuation will be derived from subject status CRF page. This analysis will be performed only on the all treated subjects population.

A by-subject listing for all treated subjects will be provided showing the subject's off treatment date and whether the subject continue in the treatment period/study along with the reason for going off treatment period/study. A by-subject listing for all enrolled subjects will also be provided, showing whether the subject was treated along with the reason for not being treated.

7.3.2 Demographics and Other Baseline Disease Characteristics

The following demographic and baseline characteristics will be summarized and/or listed by cohort:

Solid Tumor (Cohort M1, M2, and C1)

Summary:

The following subject demographics and baseline characteristics will be summarized for all treated subjects by cohort.

- Age (in years) ; age category (<65, ≥65)

- Gender
- Race
- ECOG PS
- Prior therapy (surgery, radiotherapy, systemic cancer therapy)

Listing:

- All relevant data, generally variables listed above by cohort.
- Listing of Baseline disease characteristics
- Listing of Gene Mutation Status

MM (Cohort C2)

Summary:

The following subject demographics and baseline characteristics will be summarized for all treated subjects by cohort.

- Age (in years) ; age category (<65, ≥65)
- Gender
- Race
- ECOG PS
- Prior therapy (surgery, radiotherapy, systemic cancer therapy)
- Serum M-protein (g/dL)
- Urine M-protein (mg/24 hours)
- Number of lytic bone lesions (0, 1-3, >3)
- Soft tissue plasmacytomas (Yes, No)
- Myeloma type (IgG, IgA, IgM, Light chain disease)
- ISS Stage (I, II, III)

Listing:

- All relevant data, generally variables listed above by cohort.
- Albumin (g/L) (<3.5, ≥3.5)
- LDH (<300 IU/L, ≥300 IU/L)
- Individual FISH/Cytogenetic abnormalities (del 17p, t(14; 16), t(4; 14))

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 therapy will be summarized by cohort and overall.

7.3.5 Physical Examinations

Subjects with 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 by cohort "as treated" in all treated subjects, unless otherwise specified.

7.4.1 Administration of Study Therapy

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

- Number of doses received
- Cumulative dose
- Relative dose intensity (%) using the following categories: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%

Duration of study therapy will be summarized (descriptive statistics) by cohort.

A by-subject listing of dosing of study medication (record of study medication and dose changes) will be also provided.

Table 7.4.1-1: Administration of Study Therapy - Definition of Parameters

	BMS- 986227 and Nivolumab
Dosing schedule per protocol	**BMS- 986227:** 2 mg/kg or 4 mg/kg every 2 weeks
	Nivolumab: 3 mg/kg every 2 weeks (Cohort C1, C2 only)
Dose	*Dose (mg/kg)* is defined as Total Dose administered (mg)/Most recent weight (kg). Dose administered in mg at each dosing date and weight are collected on the CRF.
Cumulative Dose	*Cum dose (mg/kg) is* sum of the doses (mg/kg) administered to a subject during the treatment period.
Relative dose intensity (%)	**BMS- 986227:**
	[Cum dose (mg/kg)/((Last dose date - Start dose date + 14) x [2 or 4 depending on planned dose level] / 14)] x 100
	Nivolumab:
	[Cum dose (mg/kg)/((Last dose date - Start dose date + 14) x 3 / 14)] x 100

Table 7.4.1-1: Administration of Study Therapy - Definition of Parameters

	BMS- 986227 and Nivolumab
Duration of study therapy	(Last dose date of any study drug - Start dose date of any study drug +14)/7, where the last dose date is event date for subjects who discontinued study therapy. Subjects who are still on therapy will be censored on their last dose date.

7.4.2 Modifications of Study Therapy

7.4.2.1 Dose Delays

Each nivolumab and BMS-986227 infusion may be delayed. A dose will be considered as actually delayed if the delay is exceeding 3 days (i.e. greater than or equal to 4 days from scheduled dosing date) for nivolumab and BMS-986227. 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 cohort:

- 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 or BMS-986227 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 by cohort:

- 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 either nivolumab or BMS-986227.

7.4.3 Dose Reductions

Dose reductions (within subject) are not permitted for either nivolumab or BMS-986227.

[redacted]

[redacted]

7.5 Efficacy

The efficacy analyses will be performed based on all treated subjects unless otherwise specified. The following will be listed by cohort.

Solid Tumor (cohort M1, M2, C1)

- Tumor lesion measurements
- Tumor evaluation at each visit
- Subject level efficacy - best overall response (BOR) and Duration of response (DOR) for responders

MM (cohort C2)

- Percent change in serum and urine M-protein, from baseline and nadir.
- Corrected Calcium results
-
- Serum and urine immunofixation test results
- Subject level efficacy - best overall response (BOR) and Duration of response (DOR) for responders

7.6 Safety

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

7.6.1 Deaths

Deaths will be summarized by cohort:

- All deaths, reasons for death.
- Deaths within 30 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 by cohort:

- 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.

All analyses will be conducted using the 30-day safety window.

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 by cohort:

- 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.

The analyses will be conducted using the 30-day safety window.

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

7.6.4 Adverse Events

Adverse events will be summarized by cohort.

The following analyses will be conducted using the 30 days safety window only:

- 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 non-serious AEs 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.

The following analyses will be conducted using the 30 days safety window and repeated using the 100 days safety window:

- 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.

7.6.5 Other Events of Interest

OEOI will be summarized by cohort for each category.

The following analyses will be conducted using the 100-day safety window:

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

A by-subject listing of OEOI will be provided.

7.6.6 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.

7.6.6.1 Hematology

The following will be summarized by cohort 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).

The analyses will be conducted using the 30-day safety window.

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

7.6.6.2 Serum Chemistry

The following will be summarized by cohort 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.

The analyses will be conducted using the 30-day safety window.

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

7.6.6.3 Electrolytes

The following will be summarized by cohort 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)

The analyses will be conducted using the 30-day safety window.

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

7.6.6.4 Abnormal Hepatic Test

Summary:

The number (%) of subjects with the following laboratory abnormalities from on-treatment evaluations will be summarized by treatment group, provided at least 5 subjects with an abnormality within at least one treatment group. Otherwise, only listing and plot will be provided:

- ALT or AST > 3 x ULN, > 5 x ULN, >10 x ULN, > 12 x ULN and > 20 x ULN
- Isolated Total bilirubin > 2 to ≤ 3 x ULN
- ALT or AST > 20 x ULN or Total bilirubin > 3 x ULN
- Concurrent (within 3 days) ALT or AST > 3 x ULN and Total bilirubin > 2 x ULN
- Concurrent (within 3 days) ALT or AST > 5 to ≤ 12 x ULN and Total bilirubin ≤ 2 x ULN
- Concurrent (within 3 days) ALT or AST > 12 to ≤ 20 x ULN and Total bilirubin ≤ 2 x ULN

Figure:

- Scatter plot of Total bilirubin peak vs AST peak
- Scatter plot of Total bilirubin peak vs ALT peak

On-treatment peak total bilirubin and on-treatment peak AST/ALT may or may not happen on the same day of liver testing.

Listing:

AST or ALT elevations, combined with a bilirubin elevation (concurrent or not) will be listed.

7.6.7 Vital Signs and Pulse Oximetry

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

7.6.8 Physical Measurements

Physical measurements will be listed by subject.

7.6.9 Immunogenicity Analysis

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.

7.6.10 Pregnancy

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

7.7 Pharmacokinetics

All available serum concentration-time data from subjects who receive BMS-986227 and/or Nivolumab will be reported. All available derived PK parameter values of BMS-986227 will be included in the PK dataset and reported, but only subjects with adequate PK profiles will be included in summary statistics and statistical analysis.

7.7.1 Contraction-Time Data

Participant concentration-time profiles will be listed and summarized by cohort and nominal collection time for BMS-986227 and Nivolumab. Overlay of individual concentration profiles over time will be provided by cohort. Plots of mean (+SD) concentration profiles versus time will be presented by cohort on the same plot.

7.7.2 PK Paramaters

Summary statistics will be tabulated for each PK parameters by cohort for BMS-986227. Geometric means and coefficients of variation will be presented for Cmax, AUC(0-t), AUC(TAU), AI_Ctrough, T-HALFeff_Ctrough. Medians and ranges will be presented for Tmax. All individual PK parameters will be listed including any exclusions.

7.7.3 Ctrough

Ctrough values will be listed and summarized by cohort and time point. To evaluate the steady state of BMS-986227 and Nivolumab concentration in the body, the geometric means of Ctrough vs. cycle will be plotted by cohort with individual participant measurements superimposed in the plots.

7.7.4 Accumulation and Effective Half-life

To assess drug accumulation over the course of dosing in this study, drug accumulation indices

$$AI = \frac{Ctrough\ on\ Cycle\ 8}{Ctrough\ on\ Cycle\ 2}$$

where k > 1 is each subsequent study day with serial PK sampling, and, if AI > 1,

effective half-lives

$$Effective\ half-life = \frac{Dose\ Interval \times \log(2)}{\log\left(AI/\left(AI-1\right)\right)}$$

will be computed for each subject and day of serial PK sampling after Day 1. If it is clear that the drug does not accumulate (AI ≤ 1), then omit effective half-lives. These values will be included in the appendix listing of PK parameters and the supplemental table of summary statistics.

[redacted]

8 CONVENTIONS

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[1]
- 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[2].
- 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 date of progression after start of study therapy, 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. In case of the date of death is present and complete, the imputed progression date will be compared to the date of death. The minimum of the imputed progression date and date of death will be considered as the date of progression.
  - If the day and month are missing or a date is completely missing, it will be considered as missing.
- For date of progression to prior therapies, 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.
  - If the day and month are missing or a date is completely missing, it will be considered as missing.
- 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.

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.

9 CONTENT OF REPORTS

The complete list of analyses contributing to the clinical study report is given in the Data Presentation Plan.

10 DOCUMENT HISTORY

Table 10-1: Document History

Version Number	[redacted]	Description
1.0		Initial version
2.0		The SAP was updated to align IO core SAP Ver 1.0.
3.0		Remove efficacy list only for MM cohort

[redacted]