Protocol Number: CA209039
IND Number: 124,055
EUDRACT Number 2018-001030-17
UTN: U1111-1210-9052
Date: 13-Mar-2012
Revised Date: 23-Apr-2019

Clinical Protocol CA209039

Multiple Phase 1/2 Cohorts of Nivolumab Monotherapy or Nivolumab Combination Regimens Across Relapsed/Refractory Hematologic Malignancies

Revised Protocol Number: 15
Incorporates Administrative Letter 10

Study Director/Central Medical Monitor

Manish Sharma, MD
[redacted]

Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Changes
Revised Protocol 15	23-Apr-2019	Major changes include: • Incorporated Administrative Letter 10 • Updated the medical monitor • Removed all references to the lirilumab/nivolumab and nivolumab monotherapy cohorts. • Removed all references to the dose selection phase. • Removed references to non-Hodgkin and Hodgkin lymphoma. • Added option for split-dosing of daratumumab at C1D1 • Added requirements for HBV DNA testing and updated requirements for hepatitis B and C criteria and testing to address daratumumab safety concerns • Clarified timing of interim and final analyses. • Deleted appendices that are no longer applicable
Administrative Letter 10	30-Apr-2018	Updated EUDRACT number and UTN. Deleted Exclusion Criteria 2., j), ii) and iii) In Table 5.1-7, in Cohort B, corrected every 4 cycles to start at cycle 9 instead of 11.
Revised Protocol 14	15-Feb-2018	Major changes: • In compliance with requests from the FDA, enrollment into the nivolumab +daratumumab with and without pomalidomide (ND±Pd: Cohort A) has been stopped. Cohort B (nivolumab +daratumumab vs daratumumab monotherapy [ND, D]) has been opened, with at 2:1 randomization. o Eligibility changes to the patient population for patients to be enrolled in Cohort B and toxicity stopping rules for the ND arm have been incorporated. o Cohort B patients (only) treated in the ND arm: Dose regimen change: nivolumab 480 mg every 4 weeks (Day 1) will begin at Cycle 2 rather than at Cycle 7 and continue until the end of treatment. Cycle 1 dose: 240 mg on Day 15. • The biomarker assessments have been aligned to the multiple myeloma program wide biomarkers evaluations. • All content related to the nivolumab +ipilimumab combination has been removed because all study procedures for this cohort, including follow-up evaluations, have been completed. Of note, Revised Protocol 13 was not activated at the study sites. All changes are further detailed in the Summary of Key Changes.

Document	Date of Issue	Summary of Changes
Revised Protocol 13	04-Aug-2017	Major changes are corrections and updates pertinent only to the nivolumab/daratumumab cohorts as follows: • Changes in eligibility for subjects with multiple myeloma (MM) for enrollment in the nivolumab/daratumumab cohorts include: – Eligible subjects must have failed prior treatment with an immune modulatory drug (IMiD) and/or a proteasome inhibitor (PI) rather than the requirement of failure to treatment with both prior treatment types. Refractory and relapsed refractory definitions removed as criterion definitions. – Subjects who received prior treatment with pomalidomide are no longer excluded from eligibility. • The randomization ratio has been changed to a 2:1 ratio, which increases the nivolumab + daratumumab + pomalidomide (ND-Pd) regimen cohort to 40 and reduces the nivolumab + daratumumab (ND) regimen cohort to 20. The sample size calculation has been updated to support change in randomization ratio. • Changes to the biomarkers plan were made to align with the program level approach and small corrections were made to the biomarkers collections schedule to ensure consistency throughout the protocol. In addition, Biomarker collections from peripheral blood specimens have been clarified to remove duplicate collections. • Daratumumab specific requirements for dose delays and discontinuation, drug preparation and administration, prevention and management of infusion related reactions, and permitted and restricted treatments have been aligned with the daratumumab IB and daratumumab standard protocol elements.
Administrative Letter 07	21-Jul-2017	Corrected inclusion criteria for subjects with MM in the nivolumab/daratumumab cohorts to accurately specify prior use of antimyeloma therapy.
Administrative Letter 06	09-Mar-2017	Corrected error on Biomarker Sampling Schedule Table 5.1-6
Revised Protocol 12	19-Jan-2017	Incorporates Amendment 13
Amendment 13	19-Jan-2017	This amendment includes corrections and updates pertinent only to the nivolumab/daratumumab cohorts. Additional biomarkers evaluations from peripheral blood specimens have been included. Daratumumab specific requirements for eligibility, dose delays and discontinuation, drug preparation and administration. Prevention and management of infusion related reactions, and permitted and restricted treatments have been aligned with the daratumumab IB and daratumumab standard protocol elements.
Administrative Letter 05	22-Nov-2016	Corrected Schedule of Assessment to align with Section 5.2.1.2 for IMWG response and provided clarification for location of bone marrow samples.
Administrative Letter	18-Oct-2016	Corrected errors in exclusion criterion for QTC prolongation and

Document	Date of Issue	Summary of Changes
04		platelet count in criteria to resume treatment with daratumumab.
Administrative Letter 03	23-Aug-2016	Clarification for inconsistencies between the age groups for dexamethasone dosing defined in the dosing schema and in protocol body, and to provide details for specific bone marrow assessments included in the IMWG response criteria.
Revised Protocol 11	09-Aug-2016	Incorporates Amendment 12
Amendment 12	09-Aug-2016	Adds an additional set of cohorts (approximately 60 additional subjects) for dose expansion in multiple myeloma patients treated with Nivolumab and Daratumumab with or without Pomalidomide and Dexamethasone
Administrative Letter 02	03-Feb-2016	Change in Study Director/Central Medical Monitor
Revised Protocol 10	01-Oct-2015	Incorporates Amendment 11
Amendment 11	01-Oct-2015	Update follow up requirements
Revised Protocol 09	15-Apr-2015	Incorporates Amendment 10
Amendment 10	15-Apr-2015	Retrospectively collect radiographic images for blinded independent central review
Revised Protocol 08	05-Feb-2015	Incorporates Amendment 09
Amendment 09	05-Feb-2015	Removes exploratory cohorts from the nivolumab/ipilimumab cohorts
Revised Protocol 07	02-Dec-2014	Incorporates Amendment 08
Amendment 08	02-Dec-2014	Revises protocol to meet FDA guidance.
Revised Protocol 06	20-Aug-2014	Incorporates Amendment 07
Amendment 07	20-Aug-2014	Adds an additional set of cohorts (approximately 80 additional subjects) for dose expansion with combination of lirilumab and nivolumab
Revised Protocol 05	19-Dec-2013	Incorporates Amendment 06
Amendment 06	19-Dec-2013	Adds an additional set of cohorts (approximately 75 additional subjects) for dose escalation and dose expansion with combination of ipilimumab and nivolumab.
Revised Protocol 04	10-Oct-2013	Incorporates Amendment 05
Amendment 05	10-Oct-2013	Includes corrections for protocol clarity.
Revised Protocol 03	25-Jun-2013	Incorporates Amendment 04
Amendment 04	25-Jun-2013	Eliminate the CML cohort in the expansion phase as recruitment would be difficult due to lack of concomitant therapy with a tyrosine kinase inhibitor and increase the size of the remaining four cohorts from 16 to 23 subjects to redistribute the allotted patients from the eliminated CML cohort.
Revised Protocol 02	06-Mar-2013	Incorporates Amendment 03
Amendment 03	06-Mar-2013	Inclusion of non-clinical safety findings related to reproductive toxicology data

Document	Date of Issue	Summary of Changes
Revised Protocol 01	21-Dec-2012	Incorporates Administrative Letter 01 and Amendment 02
Amendment 02	21-Dec-2012	Eliminate the highest (10 mg/kg) of three dose levels scheduled to be examined, require that 8 of 16 subjects with multiple myeloma be required to undergo bone marrow biopsy while on therapy, and modify the discontinuation criteria to be more stringent
Administrative Letter 01	23-May-2012	Update Medical Monitor
Original Protocol	13-Mar-2012	Not applicable

SYNOPSIS

Clinical Protocol CA209039

Protocol Title: Multiple Phase 1/2 Cohorts of Nivolumab Monotherapy or Nivolumab Combination Regimens Across Relapsed/Refractory Hematologic Malignancies

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s):

BMS-936558 (nivolumab)

- Flat dose regimen: Intravenous (IV) infusion of BMS-936558 (nivolumab) at dose of 240 mg every 2 weeks (Q2W) in Cycles 1 through 6 (Cohort A), followed by 480 mg every 4 weeks (Q4W) from Cycle 7 and beyond. Doses should be administered over a 30 minute period. Therapy will be continued until disease progression.

  Nivolumab/Daratumumab Cohort B only: Flat dose regimen: Intravenous (IV) infusion of BMS-936558 (nivolumab) at a dose of 240 mg on Cycle 1 Day 15, followed by 480 mg every 4 weeks (Q4W) from Cycle 2 and beyond (Day 1). Doses should be administered over a 30 minute period. Therapy will be continued until disease progression.

Daratumumab

- Weight based: IV infusion of daratumumab as follows:
  - Cycle 1-2: 16 mg/kg Days 1, 8, 15, 22
  - Cycle 3-6: 16 mg/kg Days 1, 15
  - Cycle 7 & beyond: 16 mg/kg, Day 1

NIVOLUMAB/DARATUMUMAB COHORTS

Per Revised Protocol 14, Cohort A (nivolumab-daratumumab with or without pomalidomide and dexamethasone) is closed to enrollment. Cohort B (nivolumab-daratumumab and daratumumab monotherapy) is open to enrollment.

Study Phase: 1

[redacted]

Objectives

Primary Objective: To establish the tolerability of the combination of nivolumab and daratumumab in subjects with relapsed/refractory MM.

Secondary Objectives:

- To assess the minimal residual disease (MRD) status for MM subjects in each treatment regimen group
- To assess overall response rates (ORR) and duration of response (DOR) for MM subjects in each treatment regimen group
- To assess progression free survival (PFS) for MM subjects in each treatment regimen group
- To characterize the immunogenicity of nivolumab when administered in combination with daratumumab
- To characterize the pharmacokinetics of nivolumab when administered in combination with daratumumab

[redacted]

[redacted]

Study Design

Per revised Protocol 14, Cohort A (ND ± Pd) is closed to enrollment. Patients who are already on treatment will continue to receive study treatment as long as they derive clinical benefit and criteria for treatment discontinuation are not met.

Cohort A is closed to enrollment per Revised Protocol 14.

Study Population:
Multiple Myeloma
Randomization 1:1

ND-Pd regimen: Multiple myeloma

Each cycle is 28 days

Nivolumab:

- Cycle 1: 240 mg iv Day 15
- Cycle 2-6: 240 mg iv Days 1, 15
- Cycle 7 & beyond: 480 mg iv Day 1

Daratumumab:

- Cycle 1-2: 16 mg/kg iv Days 1, 8, 15, 22
- Cycle 3-6: 16 mg/kg iv Days 1, 15
- Cycle 7 & beyond: 16 mg/kg iv Day 1

Pomalidomide:

- 4 mg po daily (Days 1-21) of each 28-day cycle

Dexamethasone:

Weeks without daratumumab dosing

- 40 mg po per day (Days 1, 8, 15, 22) of each 28-day cycle for subjects ≤ 75 years old
- 20 mg po per day (Days 1, 8, 15, 22) of each 28-day cycle for subjects > 75 years old

Weeks with daratumumab dosing

- 20 mg iv before the daratumumab infusion and 20 mg po after the daratumumab infusion in subjects ≤ 75 years old
- 16 mg iv before the daratumumab infusion and 4 mg po after the daratumumab infusion in subjects > 75 years old

ND regimen: Multiple myeloma

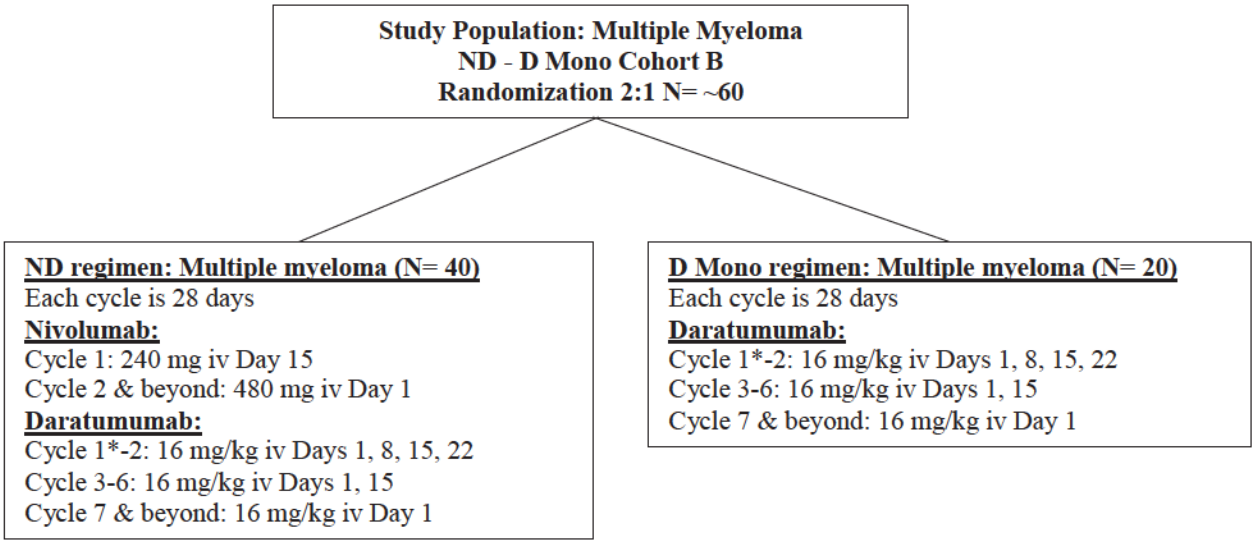
Each cycle is 28 days

Nivolumab:
Cycle 1: 240 mg iv Day 15
Cycle 2-6: 240 mg iv Days 1, 15
Cycle 7 & beyond: 480 mg iv Day 1

Daratumumab:
Cycle 1-2: 16 mg/kg iv Days 1, 8, 15, 22
Cycle 3-6: 16 mg/kg iv Days 1, 15
Cycle 7 & beyond: 16 mg/kg iv Day 1

Per Revised Protocol 14, Cohort B (ND, D) has been added to the study and is open to enrollment.

Cohort B is open for enrollment per Revised Protocol 14.



* Split dosing is available for Cycle 1 Day 1.

Study Population: MM subjects with detectable disease (serum M-protein ≥ 0.5 g/dl, OR urine M-protein ≥ 200 mg/24-hour collection sample, OR involved serum free-light chain (sFLC) ≥ 100 mg/L provided FLC ratio is abnormal), with ECOG 0-1, who either received at least 3 prior lines of therapy (including an IMiD and a PI) or are double refractory to IMiD and PI are eligible. Excluded are MM subjects with solitary bone or extramedullary plasmocytoma as only evidence of plasma cell dyscrasia, MGUS, SMM, amyloidosis, Waldenstrom's macroglobulinemia, POEMS syndrome, active plasma cell leukemia, or subjects who received any antibody or drug specifically targeting T cell co-stimulation or checkpoint pathways or anti-CD38 monoclonal antibodies.

Study Assessments

Safety Evaluation: Adverse events will be assessed continuously during the study and for 100 days post last treatment. Adverse events will be coded using the most current version of MedDRA and reviewed for potential significance and importance. Adverse events will be evaluated according to the NCI CTCAE Version 4.0.

Stopping Rules for toxicity have been incorporated in Section 3.1.1.1.

Efficacy Evaluation: Bone marrow aspirate samples for cyotmetry and molecular MRD assessments will be collected at specified time points and will be analyzed at Sponsor designated laboratories. For response, subjects will be evaluated using the modified International Myeloma Working Group (IMWG) criteria (Appendix 3). Serum and urine samples for efficacy laboratory assessments will be collected every 4 weeks from Cycle 1 Day 1 until disease progression. All response (≥ PR) and progression categories require 2 consecutive assessments for confirmation.

For Cohort B, all efficacy laboratory assessments (SPEP/SIFE), UPEP/UIFE, sFLC) will be done at a central laboratory, except for corrected calcium and disease status in bone marrow (ie, plasma cell percentage and clonality) which will be done locally. For Cohort A, local laboratories will be used for all efficacy assessments.

To assess potential daratumumab and nivolumab interference with serum M protein quantification, samples may be analyzed to distinguish daratumumab and nivolumab from endogenous myeloma protein (M protein).

Pharmacokinetic Evaluation: Sparse blood samples for nivolumab pharmacokinetic assessments will be collected from all subjects at specified time points.

Immunogenicity Evaluations: Blood samples to evaluate development of positive nivolumab anti-drug antibody (ADA) response will be collected at specified time points for all subjects.

Biomarker Evaluation: Biomarkers will be analyzed in peripheral blood and bone marrow aspirate to better understand how the immune microenvironment may contribute to immune evasion, the progression of multiple myeloma, and potential synergies between nivolumab and daratumumab. Residual sample material available after completion of the designated analyses may be used in the future for identification of additional predictive markers or to enhance understanding of disease biology.

Statistical Considerations

Sample Size:

Per Revised Protocol 14, Cohort A (ND ± Pd) is closed to enrollment, and Cohort B (ND and D) is open for enrollment.

The planned sample size for Cohort B (ND, D) will be approximately 60 treated subjects, randomized in a 2:1 ratio in favor of the ND arm.

This is a Phase 1/2 study and the sample size in Cohort B is not powered for statistical hypothesis testing but is designed to evaluate both safety profile and clinical benefit of nivolumab with daratumumab.

If the true toxicities incidence rate in a cohort is 20% then with 20 patients in D cohort, there is 7% chance of observing 0 - 1 toxicities (false negative rate). If the true toxicities incidence rate in a cohort is 5% rather than 20%, then there is 26% chance that there will be at least 2 toxicities in 20 subjects (false positive rate). If the true toxicities incidence rate in a cohort is 20% then with 40 patients there is 3% chance of observing 0 - 3 toxicities (false negative rate). If the true toxicities incidence rate in a cohort is 5% rather than 20%, then there is 14% chance that there will be at least 4 toxicities in 40 subjects (false positive rate).

In 2 daratumumab monotherapy studies in relapsed/refractory MM patients, including a Phase 1/2 dose escalation study (GEN501)[i] in patients with at least 2 lines of prior therapy and a Phase 2 study (SIRIUS)[ii] in patients with at least 3 lines of prior therapy, the ORR were 36% and 29.2% respectively.

In two combination studies in relapsed/refractory MM patients with at least 2 lines of prior therapy, including a Phase 1b study of daratumumab in combination with pomalidomide and dexamethasone [iii] and a Phase 1 dose-escalation study of pembrolizumab in combination with lenalidomide and dexamethasone,[iv] the ORR were 60%.

Table 8.1-1 summarizes the 95% exact CI for the target ORRs ranging from 30% to 80% with sample size of 20 or 40 in a cohort. At observed ORR ≥ 55% with 20 subjects, the lower bound of the 95% CI is 31.5%. At observed ORR ≥ 77.5% with 40 subjects, the lower bound of the 95% CI is 61.5%.

Table 8.1-2 summarizes the 95% exact CI for the target MRD-target negativity rates ranging from 10% to 30% with sample size of 20 or 40 in a cohort. At observed MRD-target negativity rates ≥ 30% with 20 subjects and observed MRD-target negativity rates ≥ 20% with 40 subjects, the lower bound of the 95% CI are 11.9% and 9.1% respectively compares favorably to historical MRD-target negativity rate of 8% in recurrent pretreated relapsed or refractory MM.

Endpoints:

Safety:

The primary objective is to characterize the safety and tolerability of nivolumab and daratumumab. The primary objective will be measured by:

- Number and percent of subjects that experience drug-related grade 3-4 AEs occurring up to 100 days after the last dose of study drug. [Time Frame - On a continuous basis up to 100 days after the last dose of study drug];
- Number and percent of subjects that experience drug-related grade 3-4 SAEs occurring up to 100 days after the last dose of study drug. [Time Frame - On a continuous basis up to 100 days after the last dose of study drug];
- Number and percent of subjects with clinical laboratory abnormalities by worst toxicity grade by NCI CTCAE version 4.0 (as assessed at the planned times listed in Section 5.1). [Time Frame - On a continuous basis up to 100 days after the last dose of study drug].

Efficacy: Minimal Residual Disease (MRD) negativity status, objective response rate (ORR), duration of response (DOR), progression free survival (PFS), and overall survival (OS) for all treated subjects.

Both cytometry and molecular MRD from bone marrow aspirate will be evaluated. The time point for MRD negativite status for MM subjects in the nivolumab/daratumumab cohorts is a dichotomized variable for quantifiable MRD detection.

Pharmacokinetics: Nivolumab serum concentrations at the end of a dosing interval (Cmin) and end of study drug infusion (Ceoinf) will be derived from serum concentration versus time data.

Immunogenicity: The frequency of nivolumab baseline ADA positive subjects and frequency of ADA positive subjects will be provided.

Biomarker: Additional exploratory biomarker studies will be performed as described in Section 5.7.

Analyses:

Safety Analyses: All recorded adverse events will be listed and tabulated by system organ class, preferred term, treatment, and coded according to the most current version of MedDRA. The incidence of adverse events will be reviewed for potential significance and clinical importance. Vital signs and clinical laboratory test results will be listed and summarized by treatment. Any significant physical examination findings and results of clinical laboratory tests will be listed. ECG results will be evaluated by the investigator and abnormalities, if present, will be listed.

Efficacy Analyses: Individual BOR, duration of response and PFS will be listed, using the modified International Myeloma Working Group Uniform Response Criteria. BOR outcomes will be tabulated by treatment. The ORR and corresponding 95% exact confidence interval will be provided by treatment. The median duration of response and PFSR at select time points and corresponding two-sided 95% confidence intervals will be estimated by Kaplan-Meier methodology, by treatment, depending on data availability. [redacted] Kaplan-Meier plots of PFS and overall survival will be provided by treatment. ORR, duration of response and PFS analyses will include subjects by treatment. Individual changes in the tumor burden over time may be presented graphically based on the availability of data within treatment.

MRD negativity status for MM subjects in the nivolumab/daratumumab cohorts will be evaluated by time points. The frequency of the MRD negativity status will be summarized by treatment arm. The cross tabulation of the MRD negativity status and BOR will be presented. Summary statistics of the MRD levels and their corresponding percent changes from baseline will be tabulated by planned study day by cohorts. Potential association between the first/best MRD negativity status with PFS and OS will be evaluated. Additional details will be presented in the Statistical Analysis Plan.

Pharmacokinetic Analyses: Summary statistics will be tabulated for the pharmacokinetics parameters of nivolumab by dose and study week. Pharmacokinetic concentrations of nivolumab from all subjects will be listed, and may be used in combination with other studies for exposure response or population pharmacokinetic modeling, which will be part of a separate report.

Immunogenicity Analyses: A listing will be provided of all available immunogenicity data. Additionally, a listing [redacted]

TABLE OF CONTENTS

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

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

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

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

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

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

2.2 Institutional Review Board/Independent Ethics Committee

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

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

2.3 Informed Consent

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

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

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

Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4) Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
5) If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his

or her informed consent during the study, consent must additionally be obtained from the subject.

6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed HIPAA Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is a Phase 1/2, open-label, multicenter, study of nivolumab, a fully human monoclonal IgG4 antibody targeting the PD-1 membrane receptor on T cells.

NIVOLUMAB/DARATUMUMAB COHORTS

Combination cohorts will evaluate the combination of nivolumab and daratumumab in relapsed/refractory MM patients.

Per Revised Protocol 14, Cohort A is closed to enrollment. Patients who are already on treatment in this cohort will continue to receive study treatment as long as they derive clinical benefit and do not meet the protocol defined criteria for discontinuation (Section 4.1.5). See Figure 3.1-1.

Cohort B (ND, D) has been added to the study and is open to enrollment. See Figure 3.1-2.

The study will consist of Screening (up to 28 days), Treatment (until disease progression), and Follow-up.

Figure 3.1-1: **Study Design for Cohort A (ND ± Pd)** Cohort A is closed for enrollment per Revised Protocol 14

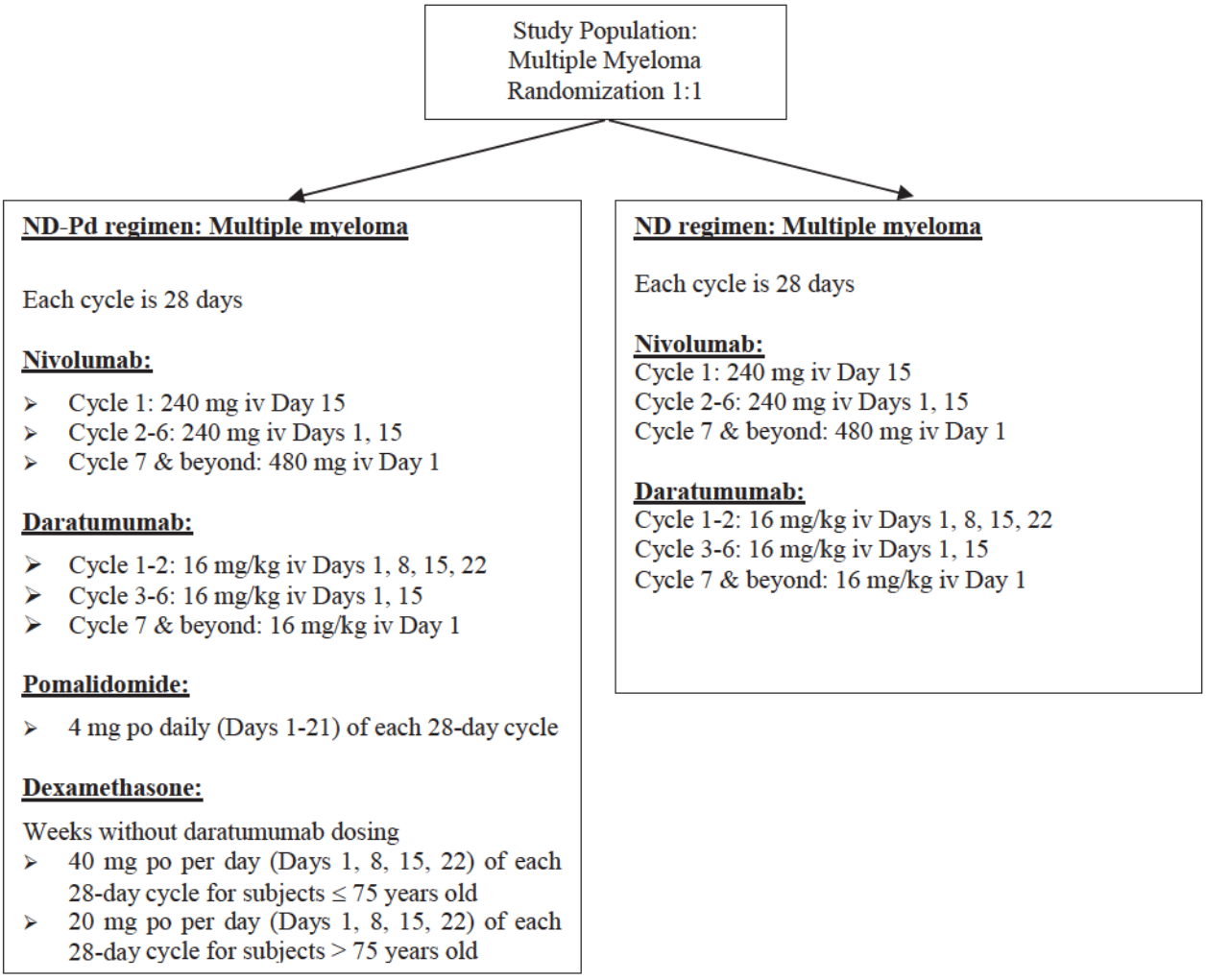
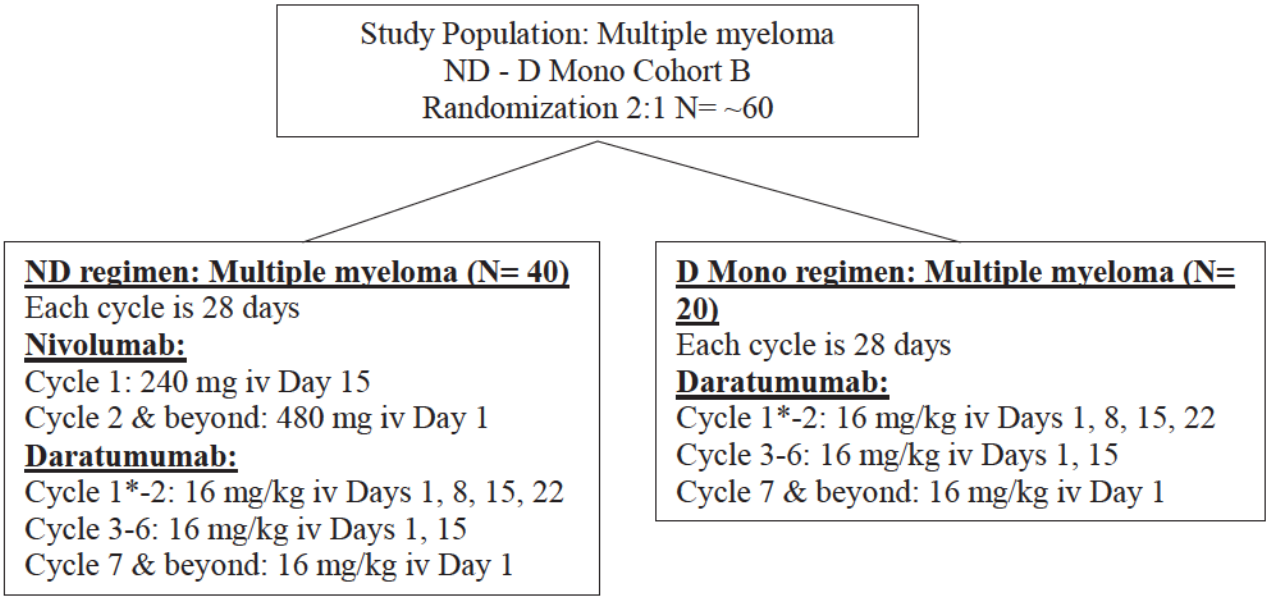


Figure 3.1-2: **Study Design for Cohort B (ND and D)** Cohort B is open for enrollment per Revised Protocol 14.



* Split dosing is available for Cycle 1 Day 1. See Section 4.1.1.2.

Dosing schematics for the nivolumab/daratumumab cohorts are provided in Appendix 6.

Approximately 60 eligible MM subjects will be enrolled in Cohort B (ND and D) and will be randomized in a 2:1 ratio in favor of the ND regimen. Subjects will continue treatment as long as the subject has clinical benefit from the treatment and does not meet criteria for treatment discontinuation.

All AE data will be monitored on an ongoing basis for safety. Stopping rules for toxicity in the nivolumab-daratumumab arm are specified in Section 3.1.1.1.

For assessment of MRD by molecular and cytometry approaches to detect disease in the bone marrow, all MM subjects will require bone marrow aspirates at the time points described in Table 5.1-6.

Bone marrow and peripheral blood samples are also needed to better understand how the immune microenvironment may contribute to immune evasion, the progression of multiple myeloma, and potential synergies between nivolumab and daratumumab. Bone marrow from every harvest should also be submitted for biomarker analysis, as described in Table 5.1-6. At the time of the scheduled bone marrow aspirate, the PI will determine if there have been significant changes in the clinical course to suggest that subjects can no longer undergo the procedure safely. Similarly, the PI will determine if there have been significant changes in the clinical course to suggest that subjects can no longer safely undergo the additional peripheral blood collection for biomarkers assessments. These subjects may continue therapy.

Clinical response will be assessed based on the modified IMWG criteria based on serum and urine laboratory assessments every 4 weeks from Cycle 1 Day 1 until disease progression,

irrespective of dose delays or treatment interruptions. All response (≥ PR) and progression categories require 2 consecutive laboratory assessments to confirm response or progression before initiation of any new therapy. If progression is confirmed at the second laboratory assessment, all study treatment will be discontinued.

To assess potential daratumumab and nivolumab interference with serum M protein quantification, samples may be analyzed to distinguish daratumumab and nivolumab from endogenous myeloma protein (M protein).

Subjects who experience AEs that require discontinuation of daratumumab may be allowed to continue therapy with nivolumab (if randomized to the ND arm), with or without pomalidomide and dexamethasone, (if randomized to the NDPd arm) if deemed in their best interest by both the PI and the BMS medical monitor. Subjects must be deriving clinical benefit.

Subjects who experience AEs that require discontinuation of nivolumab may be allowed to continue therapy with daratumumab (if randomized to ND arm), with or without pomalidomide and dexamethasone, (if randomized to NDPd arm), if deemed in their best interest by both the PI and the BMS medical monitor. Subjects must be deriving clinical benefit.

Subjects who experience AEs that require discontinuation of nivolumab and daratumumab in the ND-Pd cohort may be allowed to continue therapy with pomalidomide and dexamethasone, if deemed in their best interest by both the PI and the BMS medical monitor. Subjects must be deriving clinical benefit.

Subjects who experience AEs that require discontinuation or delay of pomalidomide in the ND-Pd cohort may be allowed to continue therapy with nivolumab, daratumumab, and dexamethasone, if deemed in their best interest by both the PI and the BMS medical monitor. Subjects must be deriving clinical benefit.

Subjects who experience AEs that require discontinuation or delay of dexamethasone in the ND-Pd cohort may be allowed to continue therapy with nivolumab, daratumumab, and pomalidomide, if deemed in their best interest by both the PI and the BMS medical monitor. Subjects must be deriving clinical benefit.

3.1.1 Stopping Rules

3.1.1.1 Stopping Rules for Toxicity in the ND Arm

The ND arm will be stopped if any of the following safety events are observed:

- Grade ≥ 3 nivolumab immune-related adverse events: ≥ 10% occurrence in the first 50% of treated patients
- Grade 5 adverse events, excluding those due to disease progression, cumulative rate: ≥ 20% occurrence in the first 50% of treated patients.

3.2 Post Study Access to Therapy

At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive study drug. Study drug will be provided via an extension of the study, a

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

3.3 Study Population

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

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

a) Voluntary signed and dated IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not a part of standard of care

2. Target Population

a) ECOG Performance of 0 or 1. (See Appendix 1)

b) Not applicable per Revised Protocol 14.

c) Not applicable per Revised Protocol 14.

d) Not applicable per Revised Protocol 14.

e) Subjects must meet the following:

i) Must have measurable disease as measured by presence of monoclonal immunoglobulin protein in a serum electrophoresis: IgG, IgA, IgM, (M-protein $\geq$ 0.5 g/dl), OR urine M-protein $\geq$ 200 mg/24-hour collection sample, OR involved serum free-light chain (sFLC) $\geq$ 100 mg/L provided FLC ratio is abnormal

ii) Must have corrected serum calcium < 11.5 mg/dL within 2 weeks of randomization

iii) Must consent to bone marrow aspirate or biopsy.

iv) Must be at least 14 days from use of prior anti-myeloma therapy (approved therapies), and at least 28 days or 5 half-lives, whichever is longer, from use of any experimental drug therapy or plasmapheresis. Bisphosphonates use is permitted if initiated prior to the first dose of study medication.

v) Must be more than 12 weeks post autologous transplant

vi) Not applicable per Revised Protocol 14

vii) Not applicable per Revised Protocol 14

viii) Not applicable per Revised Protocol 14

(1) Not applicable per Revised Protocol 13

(2) Not applicable per Revised Protocol 13

ix) No applicable per Revised Protocol 14

x) Must meet one of the criteria below:

(1) Subject has received at least 3 prior lines of therapy including a proteasome inhibitor [PI] and an immunomodulatory agent [IMiD]

OR

(2) Subject has disease that is double refractory to a PI and an IMiD*

* NOTE: Refractory is defined as disease progression on or within 60 days of treatment with a PI and an IMiD, given in the same or different lines of therapy.

f) Not applicable per Revised Protocol 14.

g) Not applicable per Revised Protocol 14.

h) Not applicable per Revised Protocol 14.

i) Not applicable per Revised Protocol 14.

j) Prior palliative radiation must have been completed at least 2 weeks prior to study Day 1

k) Toxicities related to prior therapy must have returned to Grade 1 or less, except for alopecia. Peripheral neuropathy must be Grade 1 or less.

l) Adequate bone marrow function defined as:

i) Absolute neutrophil count ≥ 1000/µl (no growth factor within 1 week of study drug administration; no pegylated growth factors within 3 weeks of first drug administration)

ii) Hemoglobin ≥ 8 g/dL. No transfusions are allowed within 72 hours prior to qualifying laboratory value. Recombinant human erythropoietin not permitted within 3 weeks of study drug administration.

iii) Platelet count ≥ 75 X 10^3/µl or > 30 x 10^3/µL if ≥ 50% of bone marrow nucleated cells were plasma cells. Qualifying laboratory value must occur at the most recent measurement prior to study entry. No transfusion to achieve this level is permitted within 72 hours prior to qualifying laboratory value.

m) Adequate renal parameters defined as:

i) Creatinine clearance (CrCl) ≥ 30 ml/min measured by 24-hour urine collection or estimated by the Cockcroft-Gault formula

ii) Adequate hepatic parameters defined as:

(1) AST < 3 x ULN

(2) ALT < 3 x ULN

(3) Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert's Syndrome, who must have a total bilirubin < 3.0 mg/dL and direct bilirubin < 0.5 mg/dL

n) Ability to comply with treatment, PK, and immune-monitoring sample collection (when indicated) and required study follow up

o) Not applicable per Protocol Amendment 12.

p) Not applicable per Revised Protocol 14

q) Not applicable per Revised Protocol 14

r) Not applicable per Revised Protocol 14

s) Not applicable per Revised Protocol 14

t) Not applicable per Revised Protocol 14

u) Not applicable per Revised Protocol 14

v) Not applicable per Revised Protocol 13

3. Age and Reproductive Status

a) (See Section 3.3.3 for the definition of WOCBP) Men and women ≥ 18 years of age

b) Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception from the time of enrollment through the duration of treatment with study drug plus 5 months after the last dose of investigational product. (See Appendix 4 for birth control instructions)

c) Women of childbearing potential (WOCBP) must have 2 negative serum or urine pregnancy tests (minimum sensitivity 25 IU/L or equivalent units of HCG): one 10-14 days prior to start of the study drug, and another within 24 hours prior to the start of study drug.

d) Women must not be breastfeeding

e) Sexually active fertile men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 7 months after the last dose of investigational product.

f) Azoospermic males and WOCBP who are not heterosexually active are exempt from contraceptive requirements. However they must still undergo pregnancy testing as described in this section.

g) Not applicable per Revised Protocol 14.

4. **Not applicable per Revised Protocol 14.**

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. At a minimum, subjects must agree to the use of two methods of contraception, with one method being highly effective and the other method being either highly effective or less effective as listed in the informed consent document.

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Not applicable per Revised Protocol 14

b) Subjects with a history of central nervous system involvement by hematologic malignancy or symptoms suggestive of central nervous system involvement

c) Not applicable per Revised Protocol 14

d) Not applicable per Revised Protocol 14

e) Subjects are excluded if they have:

i) Solitary bone or extramedullary plasmacytoma as the only evidence of plasma cell dyscrasia

ii) Monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM), primary amyloidosis, Waldenstrom's macroglobulinemia,

or POEMS syndrome (plasma cell dyscrasia with poly neuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)

iii) Active plasma cell leukemia (defined as either 20% of peripheral blood white blood cell count comprised of plasma/CD138+ cells or an absolute plasma cell count of 2 x 10^9/L)

2. Medical History and Concurrent Diseases

a) Subjects with concomitant second malignancies (except adequately treated non-melanomatous skin cancers, melanoma in situ surgically resected, carcinoma in situ of the breast, superficial bladder cancer, prostate cancer or in situ cervical cancers) are excluded unless a complete remission was achieved as it is empirically determined based on the malignancy and treatment provided prior to study entry and no additional therapy is required or anticipated to be required during the study period

b) Subjects with an active, known, or suspected autoimmune disease. Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

c) A serious uncontrolled medical disorder or active infection which would impair the ability of the subject to receive protocol therapy or whose control may be jeopardized by the complications of this therapy

d) Deep vein thrombosis not adequately controlled

e) Uncontrolled or significant cardiovascular disease including, but not limited to any of the following:

i) myocardial infarction or stroke/TIA within the past 12 months

ii) unstable or poorly controlled angina within the past 3 months

iii) any history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation or torsades de pointes)

iv) QTc prolongation > 480 msec

v) history of other clinically significant heart disease (ie, cardiomyopathy, congestive heart failure with NYHA functional classification III-IV, pericarditis, significant pericardial effusion)

vi) requirement for daily supplemental oxygen therapy

f) Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137 or anti CTLA-4 antibody (or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways).

g) Not applicable per Revised Protocol 07

h) Not applicable per Revised Protocol 011

i) Prior organ allograft or allogeneic bone marrow transplantation

j) Any of the following:

i) Prior treatment with anti CD38 monoclonal antibodies.

ii) Not applicable per Revised Protocol 14

iii) Not applicable per Revised Protocol 14

iv) Treatment with corticosteroids within 2 weeks of the first dose of study drug, except for the equivalent of ≤ 10 mg prednisone per day or corticosteroids with minimal to no systemic absorption (ie, topical or inhaled steroids) or for short course (≤ 4 days) of 40 mg dexamethasone or equivalent for emergency use (baseline M proteins must be drawn after this short course and prior to randomization). Adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease

v) Major cardiac surgery within 8 weeks prior to the first dose of study drug; all other major surgery within 4 weeks prior to the first study drug dose. Kyphoplasty is not considered major surgery; subjects should have been fully recovered from any surgical related toxicities

vi) Known chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) <50% of predicted normal.

vii) Known moderate or severe persistent asthma within the past 2 years, or uncontrolled asthma of any classification. Subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed to participate in the study.

k) Vaccination with live attenuated vaccines within 4 weeks of first study agent administration

3. Physical and Laboratory Test Findings

a) Positive for human immunodeficiency virus (HIV 1/2) antibody (may obtain additional testing or substitute testing per institutional guidelines to rule out infection), or known acquired immunodeficiency syndrome (AIDS)

b) Not applicable per Revised Protocol 15.

c) Not applicable per Revised Protocol 14.

d) Seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Subjects with resolved infection (ie, subjects who are HBsAg negative but positive for antibodies to hepatitis B core antigen [antiHBc] and/or antibodies to hepatitis B surface antigen [antiHBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. EXCEPTION: Subjects with serologic findings suggestive of HBV vaccination (antiHBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR.

e) Seropositive for hepatitis C (except in the setting of a sustained virologic response [SVR], defined as aviremia at least 12 weeks after completion of antiviral therapy).

4. Allergies and Adverse Drug Reaction

a) History of Grade 4 anaphylactic reaction to monoclonal antibody therapy

b) Not applicable per Revised Protocol 15.

c) History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins

d) Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the daratumumab formulation.

5. **Not Applicable per Revised Protocol 11.**
6. **Other Exclusion Criteria**
   a) Prisoners or subjects who are involuntarily incarcerated
   b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria. No exception to the entry criteria is permitted.

3.3.3 Women of Childbearing Potential

Women of childbearing potential (WOCBP) include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy), and who is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

*Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels.

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal.

3.4 Concomitant Treatments

Subjects are permitted the use of topical, ocular, intranasal, intra-articular, and inhalational corticosteroids (with minimal systemic absorption). Immunosuppressive doses (eg, prednisone > 10 mg/day or equivalent) and/or physiologic replacement doses of systemic corticosteroids (eg, prednisone 10 mg/day) are permitted in the context of treating AEs. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

3.4.1 Nivolumab/Daratumumab Cohorts: Concomitant Treatments

3.4.1.1 Prohibited and/or Restricted Treatments

Any systemic, anti-myeloma therapy other than the study drugs is prohibited while on study therapy. Concomitant steroids, other than weekly dexamethasone within the ND-Pd regimen, or steroids as pre- and post-infusion medication for daratumumab infusions, or steroids allowed (as defined in eligibility criteria in Section 3.3.2) are prohibited unless used to treat an AE. Guidelines for selection and use of other concomitant medications should be derived from the daratumumab, pomalidomide, and dexamethasone prescribing information.

Avoid co-administration of pomalidomide with strong inhibitors of CYP1A2 unless medically necessary. Co-administration of pomalidomide with drugs that are strong inhibitors of CYP1A2 (eg, ciprofloxacin, enoxacin and fluvoxamine) and CYP3A4/5 (eg, ketoconazole) or P-gp could increase pomalidomide exposure and should be avoided, unless medically necessary.[100] Other than study medications, administration of any therapeutic or diagnostic investigational agent (for any indication) is prohibited while on study therapy without prior Sponsor approval.

Immunosuppressive agents are prohibited (unless utilized to treat drug-related AEs).

3.4.1.2 Required Treatment

Subjects must receive antibiotic prophylaxis, per institutional guidelines or PI discretion. (See note in Section 3.4.1.1 regarding certain classes of antibiotics.)

Subjects must receive pre-infusion and post-infusion medications (Section 4.1.4.2) with each dose of daratumumab, per the currently approved (USPI)/pharmacy reference manual (See Section 3.4.1.4).[98]

All MM subjects receiving daratumumab are required to initiate oral antiviral prophylaxis to prevent herpes zoster reactivation within 1 week of starting treatment and continue for 3 months following treatment, per the currently approved (USPI)/pharmacy reference manual.[98]

In all MM subjects receiving daratumumab, Pneumocystis carinii pneumonia (PCP) prophylaxis should be considered, as per institutional guidelines.

In all MM subjects receiving daratumumab, dexamethasone and other steroids may induce gastritis. Medications to prevent gastritis are permitted per institutional guidelines, for example proton pump inhibitors (omeprazole or equivalent) or sucralfate, or H2 blockers (ranitidine or equivalent).

MM subjects receiving pomalidomide in the ND-Pd arm must receive thromboembolic prophylaxis, per institutional guidelines or PI discretion. Examples of commonly used thrombo-embolic prophylaxis medications include aspirin, low molecular weight heparin, and vitamin K antagonists.

3.4.1.3 Permitted at Investigator Discretion

IV or inhaled corticosteroids, diphenhydramine, acetaminophen/ paracetamol, leukotriene inhibitors (montelukast sodium), or long-acting bronchodilators for the management of infusion reactions. Additional supportive measures should be provided as indicated including the following:

- oxygen inhalation
- epinephrine
- oral antiviral and antimicrobial prophylaxis
- prophylactic anti-emetics
- Prevention of constipation (eg, adequate hydration, high-fiber diet, and stool softeners if needed)
- Colony stimulating factors, erythropoietin, and transfusion of platelets and red blood cells
- bisphosphonates
- antivirals
- Loperamide is recommended for the treatment of diarrhea, starting at the time of the first watery stool. The loperamide dose and regimen is according to institutional guidelines. Prophylactic loperamide is not recommended.
- Adequate hydration is recommended for prevention of myeloma-related kidney disease
- Vaccines with inactive virus

Per the ASCO 2007 Clinical Practice Guidelines,[101] bisphosphonate therapy should be administered for a period of 2 years in MM subjects. At 2 years, the investigator should seriously consider discontinuing bisphosphonates in subjects with at least stable disease, although further use is at the discretion of the investigator.

Routine clinical practice for monitoring and prevention of osteonecrosis of the jaw (ie, comprehensive dental exam, treating active oral infections, eliminating sites of high risks for oral infection, excellent oral hygiene and avoiding invasive dental procedures while on treatment) must be followed.

- Erythropoietin (EPO) or erythropoiesis stimulating agents (prior and ongoing use according to the package insert and institutional guidelines)
- Red blood cell or platelet transfusion
- Prophylactic administration of G-CSF for neutropenic subjects or therapeutic use in subjects with serious neutropenic complications (such as tissue infection, sepsis syndrome or fungal infection) may be considered at the investigator's discretion, consistent with 2006 American Society of Clinical Oncology guidelines.

For subjects who are diagnosed with HBV reactivation while on treatment, study treatment should be interrupted until the infection is adequately controlled. Upon resumption of study

treatment, concomitant antiviral prophylaxis as per local standard of care should be considered. Primary antiviral prophylaxis for HBV is permitted as per local standard of care.

3.4.1.4 Guidelines for Management of Daratumumab-Related Infusion Reactions

MM subjects treated with daratumumab will receive pre-infusion and post-infusion medication with each daratumumab infusion, according to the currently approved (USPI)/pharmacy reference manual[98] (see Section 4.1.4.2).

Management of daratumumab infusion related reactions should be done according to the currently approved (USPI)/pharmacy reference manual.[98]

Pre-infusion medication

On daratumumab infusion days, all subjects will receive the following medications up to 3 hours prior to daratumumab infusion:

- Paracetamol (acetaminophen) 650-1000 mg IV or PO
- An antihistamine (diphenhydramine 25-50 mg IV or PO, or equivalent but avoid IV use of promethazine) (see Appendix 8 for list of antihistamines that may be used)
- A corticosteroid: methylprednisolone 100 mg IV or PO or equivalent for Cycle 1 Day 1, Cycle 1 Day 2 (split dosing of daratumumab only), and Cycle 1 Day 8 and 60 mg for all subsequent doses (in the absence of IRR adverse events in the first 2 weeks). Substitutions for methylprednisolone are allowed (see Appendix 8).
- Leukotriene Inhibitor (optional) on Cycle 1 Day 1: montelukast 10 mg PO, or equivalent.

If necessary, all PO pre-infusion medications may be administered outside of the clinic on the day of the infusion, provided they are taken within 3 hours before the infusion.

Subjects randomized to ND-Pd regimen will not receive any additional corticosteroid as pre-infusion medication besides the dexamethasone dose included in the treatment regimen (See Section 4.1.4.4). The dexamethasone dose should be administered 1 hour prior to the start of daratumumab infusion and it can be administered prior to nivolumab infusion.

Subjects randomized to ND or D regimens will receive methylprednisolone 100 mg, or equivalent, administered intravenously within 1 hour of the start of daratumumab infusion. It can be administered prior to nivolumab infusion. Following the second infusion, the dose of corticosteroid may be reduced (oral or intravenous methylprednisolone 60 mg). Substitutions for methylprednisolone are allowed, please refer to Appendix 9.

Post-infusion Medication

For the prevention of delayed infusion-related reactions, all subjects will receive corticosteroid medication as described below.

Subjects randomized to the ND-Pd regimen will not receive any additional corticosteroid as post-infusion medication besides the dexamethasone dose included in the treatment regimen as specified in Section 4.1.4.4).

Subjects randomized to the ND or D regimens will receive long- or intermediate-acting corticosteroid (20 mg methylprednisolone orally or IV or equivalent in accordance with local standards) on the 2 days following all daratumumab infusions (beginning the day after the infusion). **Except for split 1st dose, please start post infusion steroid on Cycle 1 Day 3.**

In the absence of infusion related AEs after the first 3 infusions, postinfusion corticosteroids should be administered per investigator discretion

For subjects with a higher risk of respiratory complications (eg, subjects with mild asthma or subjects with COPD who have an FEV1 <80% at screening or developed FEV1 <80% during the study without any medical history) the following postinfusion medications should be considered:

Antihistamine (diphenhydramine or equivalent)

- Leukotriene inhibitor (montelukast or equivalent)
- Short-acting β2 adrenergic receptor agonist such as salbutamol aerosol
- Control medications for lung disease (eg, inhaled corticosteroids ± long-acting β2 adrenergic receptor agonists for subjects with asthma; long-acting bronchodilators such as tiotropium or salmeterol ± inhaled corticosteroids for subjects with COPD)

In addition, these at-risk subjects may be hospitalized for monitoring for up to 2 nights after an infusion. If subjects are hospitalized, then their spirometry test (FEV1) should be performed before discharge. If these subjects are not hospitalized, then a follow up telephone call should be made to monitor their condition within 48 hours after all infusions. If no infusion-related reaction has occurred, the follow-up telephone call 48 hours after the infusion is not required. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as a serious adverse event. Investigators may prescribe bronchodilators, H1-antihistamines, and corticosteroids that are deemed necessary to provide adequate supportive care in the event a bronchospasm occurs after subjects are released from the hospital/clinic. If an at-risk subject experiences no major infusion-related reactions, then these post-infusion medications may be waived after 4 doses at the investigator's discretion.

Any post-infusion medication will be administered after the infusion has completed.

Management of Infusion-Related Reactions

- Subjects should be carefully observed during daratumumab infusions. Trained study staff at the clinic should be prepared to intervene in case of any infusion reactions, and resources necessary for resuscitation must be available. Attention to staffing should be considered when multiple subjects will be dosed at the same time.

- For infusion reactions of any grade/severity, immediately interrupt the daratumumab infusion and manage symptoms. Management of infusion reactions may further require reduction in the rate of infusion, or treatment discontinuation of daratumumab.
- Grade 1-2 (mild to moderate): Once reaction symptoms resolve, resume the infusion at no more than half the rate at which the reaction occurred. If the patient does not experience any further reaction symptoms, infusion rate escalation may resume at increments and intervals as appropriate as outlined in Table 4.1.4.2-1.
- Grade 3 (severe): Once reaction symptoms resolve, consider restarting the infusion at no more than half the rate at which the reaction occurred. If the subject does not experience additional symptoms, resume infusion rate escalation at increments and intervals as outlined in Table 4.1.4.2-1. Repeat the procedure above in the event of recurrence of Grade 3 symptoms. Permanently discontinue daratumumab upon the third occurrence of a Grade 3 infusion-related reaction.
- Grade 4 (life threatening): Permanently discontinue daratumumab treatment.

3.4.1.5 Surgery and Radiation

Use of radiotherapy or surgical intervention must be recorded on the appropriate Case Report Form. Localized radiation therapy to a site of pre-existing disease is permitted while on study.

Following approval by the medical monitor, the subject may continue with protocol therapy without interruption during the course of palliative radiation therapy if the investigator believes that the risk of excessive bone marrow suppression or other toxicity is acceptable, and it is in the best interest of the subject to do so.

If the subject develops a definite increase in the size of existing bone lesions or soft tissue plasmacytomas that meets the criteria for disease progression (see Appendix 3) treatment must be discontinued for progressive disease regardless of whether radiation therapy is initiated (Section 3.5).

3.4.2 Other Restrictions and Precautions

3.4.2.1 Treatment of Infusion Reactions

Infusion reactions should be graded according to CTCAE Version 4.0 allergic reaction/hypersensitivity. These reactions may manifest with signs and symptoms that may include, but are not limited to fever, chills, headache, rash, pruritus, arthralgias, hypo-or hypertension, bronchospasm or other symptoms. Severe infusion reactions require the immediate interruption of study drug therapy and permanent discontinuation from further treatment. Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Subjects should be carefully observed until the complete resolution of all signs and symptoms. Following an infusion reaction, subjects should be premedicated with acetaminophen and diphenhydramine for future treatments.

Nivolumab contains only human immunoglobulin protein sequences, and is therefore unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as a SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE (version 4.0) guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate.

3.4.2.2 Guidelines for Nivolumab-related Infusion Reactions

For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated)

Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional nivolumab administrations.

For Grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for ≤ 24 hours):

- Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensure after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further nivolumab will be administered at that visit.
- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before nivolumab infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms: (Severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]. Grade 4: life-threatening; pressor or ventilatory support indicated):

- Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. **Nivolumab will be permanently discontinued.** Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms.

In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

3.5 Discontinuation of Subjects from Treatment

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

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical AE, abnormal laboratory test results or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Grade 3 or 4 uveitis related to nivolumab
- Pregnancy
- Termination of the study by BMS
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- Documented and confirmed disease progression or clinical deterioration while receiving active study therapy
- Stopping rules as defined in Section 3.1.1.1.
- Severe nivolumab immune-mediated adverse events, as described in Appendix 5.

3.5.1 Additional Discontinuation Criteria - Nivolumab/Daratumumab Cohorts

In addition to the criteria defined above, subjects in the nivolumab/daratumumab cohorts (Cohort A and B) must discontinue study treatments for any of the following reasons:

- Confirmed progressive disease according to IMWG criteria (Appendix 3).
- Subjects who receive any non-protocol specified systemic anti-myeloma therapy before documented progression will be discontinued from all study treatment; however, tumor assessments will continue at 4-week intervals until documented progression.

- Subjects experiencing a Grade 4 infusion reaction related to daratumumab must discontinue daratumumab. Subjects may continue nivolumab with or without pomalidomide and dexamethasone treatment. Refer to Section 4.1.5.2 for additional reasons to discontinue daratumumab dosing permanently.
- Subjects experiencing treatment related angioedema, Grade 4 rash, exfoliative or bullous rash, Stevens Johnson syndrome, or toxic epidermal necrolysis must discontinue pomalidomide and nivolumab. Subjects may continue on daratumumab and dexamethasone.
- Subjects experiencing ≥ 8-week delay in all study drugs (nivolumab, daratumumab, pomalidomide, and dexamethasone) due to an AE(s) related to study treatment must be discontinued from all study treatment. Subjects experiencing delays unrelated to study therapy, for example due to radiation therapy, may delay study treatment up to 84 days. Further delays may be allowed after discussion with the BMS Medical Monitor.
- Subjects experiencing a Grade 4 or the third occurrence of a Grade 3 daratumumab infusion reaction must permanently discontinue daratumumab
- Subjects experiencing a Grade 3 or 4 infusion reaction related to nivolumab must discontinue nivolumab. Subjects may continue daratumumab with or without pomalidomide and dexamethasone treatment. Refer to Section 4.1.5.1 for additional reasons to discontinue nivolumab dosing permanently.

Continuation of study treatments in the circumstance of one or more study treatments being discontinued or delayed should follow these criteria:

- Subjects who experience AEs that require discontinuation of daratumumab may be allowed to continue therapy with nivolumab, with or without pomalidomide and dexamethasone, if deemed in their best interest by both the PI and the BMS medical monitor. Subjects must be deriving clinical benefit.
- Subjects who experience AEs that require discontinuation of nivolumab may be allowed to continue therapy with daratumumab, with or without pomalidomide and dexamethasone, if deemed in their best interest by both the PI and the BMS medical monitor. Subjects must be deriving clinical benefit.
- Subjects who experience AEs that require discontinuation of nivolumab and daratumumab in the ND-Pd arm may be allowed to continue therapy with pomalidomide and dexamethasone, if deemed in their best interest by both the PI and the BMS medical monitor. Subjects must be deriving clinical benefit.
- Subjects who experience AEs that require discontinuation or delay of pomalidomide in the ND-Pd arm may be allowed to continue therapy with nivolumab, daratumumab, and dexamethasone, if deemed in their best interest by both the PI and the BMS medical monitor. Subjects must be deriving clinical benefit.
- Subjects who experience AEs that require discontinuation or delay of dexamethasone in the ND-Pd arm may be allowed to continue therapy with nivolumab, daratumumab, and pomalidomide, if deemed in their best interest by both the PI and the BMS medical monitor. Subjects must be deriving clinical benefit.

All subjects who discontinue should comply with protocol specified follow-up procedures as outlined in Section 5. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If a subject was withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate case report form (CRF) page.

3.6 Post Study Drug Follow-up in Nivolumab/Daratumumab Cohorts (Cohorts A and B)

PFS and OS are efficacy endpoints of the study. Post treatment study follow-up is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study treatment prior to progression must continue to be followed for collection of protocol-defined PFS.

Subjects who discontinue study therapy may also continue to be followed for OS data.

BMS may request that survival data be collected on all treated/randomized subjects outside of the protocol-defined window. At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contacts or is lost to follow-up.

3.6.1 Withdrawal of Consent

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

3.6.2 Lost to Follow-Up

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

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact

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

4 TREATMENTS

Study drugs include both Noninvestigational (NIMP) and Investigational Medicinal Products (IMP) and can consist of the following:

- All products, active or placebo, being tested or used as a comparator in a clinical trial
- Study required premedication, and
- Other drugs administered as part of the study that are critical to claims of efficacy (eg, backbone therapy, rescue medications)

Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, investigational product(s) is/are: nivolumab and daratumumab.

Noninvestigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as noninvestigational products.

Handling and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the sponsor. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact the sponsor immediately.

Investigational product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

For nivolumab and daratumumab, please refer to the current IB/pharmacy reference sheets for storage, handling and preparation instructions.

4.1 Study Treatments - Nivolumab/Daratumumab Cohorts

For product descriptions see Table 4.1-1. Non-investigational medicinal product will be used to treat infusion reactions as described in Section 3.4.2.1.

Table 4.1-1: Product Description - Nivolumab/Daratumumab Cohorts, Treatment Period

Product Description and Dosage Form	Potency	IP/ Non IP	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
BMS-936558-01 (nivolumab) Solution for injection	100 mg (10 mg/mL)	IP	10 mL vial/ Open-Label	5 or 10 vials per carton/ Open-Label	Clear to opalescent, colorless to pale yellow liquid. May contain particles.	2 - 8°C Protect from light and freezing.
Pomalidomide Capsules*	1 mg, 2 mg, 3 mg, and 4 mg	Non IP	Market Product Configuration	Market Product Configuration	As per US commercial product.	As per Package Insert
Daratumumab Injection for Intravenous Infusion	100 mg (20 mg/mL) and/or 400 mg (20 mg/mL)	IP	Vial	Carton	Colorless to pale yellow solution in a vial.	As per Package Insert/ clinical supply label
Dexamethasone Solution**	4 mg/mL, 8 mg/mg, or other strengths	Non IP	Various Packaging Configurations	Various Packaging Configurations	Various	As per Package Insert
Dexamethasone tablets**	2 mg, 4 mg, or other strengths	Non IP	Various Packaging Configurations	Various Packaging Configurations	Various	As per Package Insert

IP= investigational product

*Pomalidomide should be obtained by the investigator sites standard prescribing procedures where allowed.

**Dexamethasone solution and tablets will be procured by the investigative sites.

4.1.1 Investigational Product

4.1.1.1 Nivolumab in the Nivolumab/Daratumumab Cohorts

Cohort A subjects: nivolumab will be administered at a dose of 240 mg as an intravenous infusion over 30 minutes every 2 weeks (Day 15 of Cycle 1, and Days 1 and 15 of each 28 day cycle during Cycles 2 through 6). Starting Cycle 7 and beyond, nivolumab will be administered at a dose of 480 mg as an intravenous infusion over 30 minutes every 4 weeks (Day 1 of each 28 day cycle).

Cohort B subjects: randomized to ND treatment (only): nivolumab will be administered at a dose of 240 mg as an intravenous infusion over 30 minutes on Day 15 of Cycle 1. Starting Cycle 2 and beyond, nivolumab will be administered at a dose of 480 mg as an intravenous infusion over 30 minutes every 4 weeks (Day 1 of each 28 day cycle).

Please refer to the nivolumab investigator brochure and/or pharmacy reference sheet/manual for guidelines on drug preparation and administration. Flush the intravenous line at the end of infusion.

4.1.1.2 Daratumumab

Daratumumab injection for IV infusion is considered IMP for this study. Daratumumab vials must be stored in accordance with the package insert (USPI) /clinical supply labeling.[70]

Daratumumab is an immunoglobulin G1 kappa (IgG1κ) human monoclonal antibody against CD38 antigen, produced in a mammalian cell line (Chinese Hamster Ovary [CHO]) using recombinant DNA technology. The molecular weight of daratumumab is approximately 148 kDa.

Daratumumab is supplied as a colorless to pale yellow preservative-free solution for intravenous infusion in single-dose vials. Daratumumab must be diluted with 0.9% Sodium Chloride Injection, USP and to be administered as IV infusion according to the infusion rates specified in the (USPI)/pharmacy reference manual.[70]

Daratumumab can cause severe infusion reactions, where about half of all patients in the studies to date experienced a reaction, most during the first infusion. Infusion reactions can also occur with subsequent infusions. Nearly all reactions occurred during infusion or within 4 hours of completing the daratumumab infusion.

Because of this high risk of infusion related reactions daratumumab infusions will be administered per the approved (USPI)/pharmacy reference manual[70] by a healthcare professional, with immediate access to emergency equipment and appropriate medical support to manage infusion reactions if they occur, and all subjects will receive pre-infusion and post-infusion medication per the approved (USPI)/pharmacy reference manual.[70]

Before administration the drug product should be stored and prepared as per the instructions in current (USPI)/pharmacy reference manual.[70] The dose of daratumumab to be administered to a

subject will be calculated by multiplying the subject's weight (kg) by 16 mg/kg. The subject's predose weight on Day 1 of each cycle will be used to calculate the dose for each cycle. The dose does not need to be recalculated for weight changes that are < 10% from baseline. Each dose should be infused as per instructions in the current daratumumab (USPI)/pharmacy reference manual.[70]

For the administration of the first 16 mg/kg dose of daratumumab, in additional to previously approved single first infusion on Cycle 1 Day 1, a split-dosing regimen (ie, splitting the first dose over two consecutive days at 8 mg/kg on Cycle 1 Days 1 and 2) was recently approved in EU, US, and Canada. Investigators are allowed to opt for the split-dosing regimen.

The infusion start and stop time will be recorded in the CRF. If the infusion is stopped mid-session for any reason, the stop/start time must be recorded together with an explanation.

Indirect Antiglobulin Test (IAT)

Blood Type, Rh, and IAT should be done before the first dose of daratumumab. Subject RBC phenotyping (standard or extended) is an alternative option to the IAT test, if locally required. Either method must be completed prior to first daratumumab infusion.

Daratumumab interferes with the Indirect Antiglobulin Test (IAT), which is a routine pre-transfusion test performed to identify a patient's antibodies to minor antigens so that suitable donor blood can be given for transfusion. Daratumumab does not interfere with /RhD typing. CD38 is expressed at very low levels on erythrocytes. Daratumumab binds to the CD38 on erythrocytes, which results in a positive IAT (also known as the Indirect Coombs Test). This positive result masks the detection of antibodies to minor antigens and may prevent or delay blood banks from issuing donor blood for transfusion. This effect occurs during daratumumab treatment and for up to 6 months after treatment ends. Subjects will receive a patient identification wallet card for the study that includes the blood profile (ABO, Rh, and IAT or phenotyping) determined before the first infusion of daratumumab along with information on the IAT interference for healthcare providers/blood banks. Subjects are to carry this card throughout the treatment period and for at least 6 months after treatment ends. Blood banks can eliminate the daratumumab IAT interference with IAT by treating reagent RBCs with dithiothreitol (DTT).[102]

Possible methods for blood banks to provide safe RBCs for transfusion to subjects receiving daratumumab include:

1) Providing ABO/RhD compatible, phenotypically (standard or extended phenotyping) or genotypically matched units
2) Providing ABO/RhD compatible, K-negative units after ruling out or identifying alloantibodies using DTT-treated reagent RBCs.

Uncrossmatched, ABO/RhD compatible RBC units should be administered if transfusion is needed emergently as per local blood bank practice.

Despite daratumumab binding to CD38 on erythrocytes, no indication of clinically significant hemolysis has been observed in daratumumab studies. For additional details, refer to the Daratumumab IB/package insert.

4.1.2 Noninvestigational Product

In this protocol, non-investigational products consist of:

- Pomalidomide (Pomalyst®) capsules 1 mg, 2 mg, 3 mg, and 4 mg
- Dexamethasone tablets and concentrate for solution for IV infusion
- Products used for daratumumab pre- and post-infusion medication (refer to Section 3.4.1.4 and (USPI)/pharmacy reference manual).[98]

4.1.2.1 Pomalidomide

Pomalidomide is an analogue of thalidomide. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If pomalidomide is taken during pregnancy, it may cause birth defects or death to an unborn baby. Females must not get pregnant: (1) for at least 4 weeks before starting pomalidomide, (2) while taking pomalidomide, (3) during any interruptions in pomalidomide treatment and (4) for at least 4 weeks after their last dose of pomalidomide. Furthermore, subjects taking pomalidomide should refrain from donating blood (until at least 90 days) or sperm (until at least 4 weeks) after last dose of pomalidomide.

Because of this potential toxicity and to avoid fetal exposure to pomalidomide, pomalidomide is only available under a special restricted distribution program. Each risk management program is country or region specific. Under these programs, only prescribers and pharmacists registered with the program can prescribe and dispense the product. In addition, pomalidomide must only be dispensed to subjects who are registered and meet all the conditions of the local pomalidomide risk management program or meet all the conditions of the Pomalidomide Pregnancy Risk Prevention Plan. Subjects who have the potential of pregnancy must be instructed about contraception and undergo the scheduled pregnancy tests. Pomalidomide should be taken in accordance with local label.

WOCBP must have negative pregnancy testing and must use contraception methods before initiating pomalidomide.

4.1.2.2 Dexamethasone

Dexamethasone tablets and solution for IV infusion is considered non-IMP for this study. Marketed product will be utilized for this study and should be stored in accordance with the package insert.[103]

4.1.3 Study Drug Storage, Preparation and Administration

Please refer to the current version of the IB and/or pharmacy reference sheets for complete storage, handling, dispensing, and infusion information for nivolumab, and to the current (USPI)/pharmacy reference manual[98] for daratumumab, and dexamethasone IV.

Nivolumab vials must be stored at a temperature of 2° to 8°C and should be protected from light and freezing. If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves. For details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration, please refer to the nivolumab IB section for "Recommended Storage and Use Conditions" and/or pharmacy reference sheets.

Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding polyethersulfone membrane in-line filter at the protocol-specified doses. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 1 mg/mL. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

Daratumumab infusion solution will be prepared as a 1,000-mL (first dose, unless using split dose) or 500-mL (second and subsequent doses) dilution of daratumumab in sterile, pyrogen-free 0.9% Sodium Chloride Injection, USP. Preparation of infusion bags should be done on the day of the planned infusion. Daratumumab must be administered as an IV infusion given through a well-functioning IV catheter by using an infusion pump or syringe pump. Daratumumab must be filtered by using an inline filter (0.2 µM) during the infusion. Manuals with detailed descriptions for preparation and administration of daratumumab will be supplied to each pharmacy and site.

In addition to administering a full dose of 16 mg/kg on Cycle 1 Day 1, "split-dosing" of daratumumab (ie, 8 mg/kg on Cycle 1 Day 1 and 8 mg/kg on Cycle 1 Day 2) can be utilized for Cohort B at the investigator's discretion. The first split-dose infusion will be prepared as a 500-mL dilution of 8 mg/kg of daratumumab given on Days 1 and 2 of Cycle 1. If these 2 infusions are well-tolerated (absence of > Grade 1 IRR), the second week of daratumumab will be given as a 16 mg/kg dose diluted in 500 cc of normal saline. If the first 2 doses of daratumumab are not well-tolerated (defined as > Grade 1 IRR), then the second week of daratumumab will be given as 16 mg/kg in 1000 mL on Cycle 1 Day 8. From Cycle 1 Day 15 and beyond, the dose of daratumumab will not be split and will be the standard 16-mg/kg dose. The dilution will be in 1000 cc of normal saline until the subject completes an infusion without > Grade 1 IRR. For all infusions, daratumumab will be prepared in sterile, pyrogen free 0.9% NaCl. Preparation of the infusion bags should be done on the day of the planned infusion. Daratumumab must be administered as an IV infusion given through a well-functioning IV catheter by using an infusion pump. The study drug must be filtered by using an inline filter (0.2 µM) during the infusion. Manuals with detailed descriptions for preparation and administration of daratumumab will be supplied to each pharmacy and site.

Infusion-related supplies (eg, IV bags, in-line filters, 0.9% NaCl solution, pump) will not be supplied by the sponsor and should be purchased locally if permitted by local regulations.

When more than one study drugs are to be administered as IV infusion on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the daratumumab infusion. The second infusion will always be daratumumab and will start no sooner than 30 minutes after completion of the nivolumab infusion.

4.1.4 Selection and Timing of Dose for Each Subject

4.1.4.1 Nivolumab

Cohort A

- Nivolumab will be administered at a dose of 240 mg as an intravenous infusion over 30 minutes on Day 15 during Cycle 1, and on Days 1 and 15 during Cycles 2 through 6 (ie, every 2 weeks of each 28-day cycle). Starting Cycle 7 and beyond, nivolumab will be administered at a dose of 480 mg as an IV infusion over 30 minutes every 4 weeks (Day 1 of each 28-day cycle).
- Nivolumab can be delayed within a 3-day window of Day 1 and Day 15, during Cycles 1 through 6, as long as the 12-day interval between 2 nivolumab doses is respected. During Cycles 7 and beyond, nivolumab can be delayed within a week, as long as the 21-day interval between 2 nivolumab doses is respected. Doses that fall outside the allowed window should be skipped.

Cohort B

- Patients randomized to ND treatment (only): nivolumab will be administered at a dose of 240 mg as an intravenous infusion over 30 minutes on Day 15 of Cycle 1. Starting Cycle 2 and beyond, nivolumab will be administered at a dose of 480 mg as an intravenous infusion over 30 minutes every 4 weeks (Day 1 of each 28 day cycle).
- Cycle 1 dose (C1D15) can be delayed within a 3 day window from Day 15. Doses that fall outside the allowed window should be skipped.
- From Cycle 2 (C2D1) and beyond, nivolumab can be delayed within in a 7 day window of Day 1, as long as the 21-day interval between two 480 mg nivolumab doses is respected, and a 12-day interval between C1D15 and C2D1 is respected. Doses that fall outside the allowed window should be skipped.

Nivolumab should be administered before daratumumab. There are no pre-medications recommended for nivolumab.

Subjects should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, subjects should be managed according to Section 3.4.2.1.

There will be no dose escalations or reductions of nivolumab allowed. Doses of nivolumab may be interrupted, delayed, or discontinued depending on how well the subject tolerates the treatment.

4.1.4.2 Daratumumab

Daratumumab will be administered at a dose of 16 mg/kg as an IV infusion every week (Days 1, 8, 15, and 22 of each 28-day cycle) during Cycles 1 and 2. As an option, in Cycle 1, the first full dose of daratumumab at 16 mg/kg may be split into 2 doses at 8 mg/kg and administered via IV on Cycle 1 Days 1 and 2. From Cycles 3 through 6, daratumumab will be administered every 2 weeks (Days 1 and 15 of each 28-day cycle), then starting Cycle 7 and beyond, daratumumab will be administered every 4 weeks (Day 1 of each 28-day cycle). The infusion rates should closely follow the specifications of the currently approved (USPI)/pharmacy reference manual.[98]

All infusions will be planned as outpatient visits. Subjects will receive preinfusion medications and postinfusion medications as detailed in the protocol.

Daratumumab should be administered after nivolumab.

MM subjects randomized to the ND or D regimens will receive pre- and post-infusion medication for daratumumab infusion per the daratumumab label, as described (in Section 3.4.1.4.

MM subjects randomized to ND-Pd regimen will receive the treatment regimen dexamethasone dose split as IV pre-infusion and oral post-infusion on weeks with daratumumab infusions, and only oral in the weeks without daratumumab infusion (see Section 4.1.4.4). No additional corticosteroids besides the dexamethasone dose included in the treatment regimen will be administered to the ND-Pd subjects.

The dilution volumes and infusion rates for C1D1 (16 mg/kg), and optional split-dosing of C1D1 (8 mg/kg) and C1D2 (8 mg/kg), C1D8 (16 mg/kg), and subsequent infusions are provided in Table 4.1.4.2-1. The sponsor may modify the infusion rates or the preinfusion medications prospectively based upon the information collected to date from this and other studies. Additional details for administration times and rates, as well as preinfusion medications, will be provided in the administration guidelines (study site investigational product and procedures manual/package insert).

Table 4.1.4.2-1: Daratumumab Infusion Rates

	Dilution Volume	Initial Infusion Rate (first hour)	Increments of Infusion Rate	Maximum Infusion Rate
C1D1 (16 mg/kg single dose)	1000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Optional split-dosing: C1D1 and C1D2 (8 mg/kg split dose)	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour

Table 4.1.4.2-1: Daratumumab Infusion Rates

	Dilution Volume	Initial Infusion Rate (first hour)	Increments of Infusion Rate	Maximum Infusion Rate
C1D8[a,b] (16 mg/kg)	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent infusions[c]	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

[a] If the subject's first infusion of daratumumab at 16 mg/kg is well-tolerated, subsequent infusions will be administered at an initial rate of 100 mL/hour and increased by 50-mL/hour increments at 60-minute intervals, as tolerated, to a maximum rate of 200 mL/hour.

[b] If the subject's first 2 infusions of 8 mg/kg daratumumab are well-tolerated (defined as an absence of IRR >Grade 1), the first infusion of 16 mg/kg daratumumab will be administered at an initial rate of 50 mL/hour and increased by 50-mL/hour increments at 60-minute intervals, as tolerated, to a maximum rate of 200 mL/hour. If the 8 mg/kg infusions are not well-tolerated (defined as IRR >Grade 1), the dose on C1D8 should be given in 1000 mL.

[c] Modified rates should only be used if the first 2 16 mg/kg infusions of daratumumab were well-tolerated as defined by an absence of > Grade 1 infusion-related reactions during a final infusion rate of ≥100 mL/hr

Vital signs should be monitored extensively throughout daratumumab infusion(s) on Cycle 1 Day 1 (16 mg/kg) or Cycle 1 Days 1 & 2 (split-dosing at 8 mg/kg). For subsequent infusions, vital signs should be measured before the start of the infusion and at the end of the infusion. If a subject experiences any significant medical event, then the investigator should assess whether the subject should stay overnight for observation. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as a serious adverse event.

There will be no dose escalations or reductions of daratumumab allowed. Doses of daratumumab may be interrupted, delayed, or discontinued depending on how well the subject tolerates the treatment.

4.1.4.3 Pomalidomide in the ND-Pd Cohort (Cohort A)

Pomalidomide will be administered orally at the dose of 4 mg daily on Days 1 - 21 of each 28-day cycle. Pomalidomide should be taken without food (at least 2 hours before or 2 hours after a meal).

Subjects should be instructed that if a dose of pomalidomide has been missed and it has been less than 12 hours since the subject's regular dosing time, to take pomalidomide as soon as the subject remembers. If it has been more than 12 hours, the dose must be skipped. Subjects should not take 2 doses at the same time.

4.1.4.4 Dexamethasone in the ND-Pd Cohort (Cohort A)

At the investigator's discretion, the oral dexamethasone dose may be given as a split dose over 2 consecutive days each week.

The administration of dexamethasone is summarized in Table 4.1.4.4-1.

Table 4.1.4.4-1: Dexamethasone Dosing

Age	Day 1	Day 8	Day 15	Day 22
Cycles 1-2				
≤ 75 years old	20 mg IV before daratumumab infusion 20 mg PO after daratumumab infusion			
> 75 years old	16 mg IV before daratumumab infusion 4 mg PO after daratumumab infusion			
Cycles 3-6				
≤ 75 years old	20 mg IV before daratumumab infusion 20 mg PO after daratumumab infusion	40 mg PO	20 mg IV before daratumumab infusion 20 mg PO after daratumumab infusion	40 mg PO
> 75 years old	16 mg IV before daratumumab infusion 4 mg PO after daratumumab infusion	20 mg PO	16 mg IV before daratumumab infusion 4 mg PO after daratumumab infusion	20 mg PO
Cycle 7 and Beyond				
≤ 75 years old	20 mg IV before daratumumab infusion 20 mg PO after daratumumab infusion	40 mg PO	40 mg PO	40 mg PO
> 75 years old	16 mg IV before daratumumab infusion 4 mg PO after daratumumab infusion	20 mg PO	20 mg PO	20 mg PO

On weeks with daratumumab infusion, dexamethasone will be administered as a split dose as described in Table 4.1.4.4-1. The IV dose can be administered approximately 1 hour prior to every daratumumab infusion (can be administered before nivolumab infusion).

On weeks without daratumumab infusion, dexamethasone will be administered orally only as described in Table 4.1.4.4-1.

If daratumumab dosing is skipped or discontinued, dexamethasone will be administered orally as in weeks without daratumumab.

4.1.5 Dose Delay, Interruption, or Discontinuation

If the dose of nivolumab, daratumumab, pomalidomide and/or dexamethasone is interrupted or discontinued, the treatment with the other drugs may continue as scheduled if deemed in their

best interest by both the PI and the BMS medical monitor. Subjects must be deriving clinical benefit.

Each cycle is 28 days. While dose delays (within the allowed window determined below for nivolumab and daratumumab) or interruptions are permitted, the start of each cycle cannot be delayed and is fixed (ie, anchored) relative to Cycle 1 Day 1. Adjustments to the Cycle 1 Day 1 anchored schedule should not be performed. Should the start of a cycle be delayed, it is expected the following cycle begin as anchored to Cycle 1 Day 1. Delayed doses which fall outside of the allowed window for delay for the respective cycle should be skipped. Subjects may continue on study therapy even if components of the study therapy must be discontinued.

Please consult the BMS Medical Monitor or any questions regarding dose interruption or study therapy discontinuation.

4.1.5.1 Nivolumab

Cohort A

During Cycles 1 through 6, subjects may be dosed no less than 12 days from the previous dose. Nivolumab can be delayed within a 3-day window of Day 1 and Day 15 as long as the 12-day interval between 2 nivolumab 240 mg doses is respected. Doses that fall outside the allowed window should be skipped.

The first dose in Cycle 7 (Day 1) may be dosed no less than 12 days from the previous dose and for subsequent doses it should be dosed no less than 21 days from the previous dose. From Cycle 7 and beyond, nivolumab can be delayed within a 7-day window of Day 1 as long as the 12-day and 21-day intervals for the first 480 mg dose and subsequent 480 mg doses, respectively, between 2 nivolumab doses is respected. Doses that fall outside the allowed window should be skipped.

Cohort B

Cycle 1 dose (C1D15) can be delayed within a 3 day window from Day 15. Doses that fall outside the allowed window should be skipped.

From Cycle 2 (C2D1) and beyond, nivolumab can be delayed within a 7 day window from Day 1, as long as the 21-day interval between two 480 mg nivolumab doses is respected, and a 12-day interval between C1D15 and C2D1 is respected. . Doses that fall outside the allowed window should be skipped.

Nivolumab Dose Delays Due to AEs

Nivolumab administration should be delayed for the following:

- Grade 2 non-skin, drug-related AE, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities
- Grade 3 skin, drug-related AE
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay

  - Grade ≥ 3 AST, ALT, Total Bilirubin will require dose discontinuation
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Participants who require delay of nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab dosing when re-treatment criteria are met.

Criteria to Resume Treatment with Nivolumab

In order to initiate a new infusion of nivolumab the following criteria must be met:

- Platelet count ≥ 25 x 10^9/L (platelet transfusion support is allowed)
- ANC ≥ 0.50 x 10^9/L (growth factor support is strongly recommended if ANC < 1.0 x 10^9/L)

Subjects may resume treatment with nivolumab when the drug-related AE(s) resolve(s) to Grade ≤ 1 or baseline, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays/interruptions for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters should have treatment permanently discontinued
- Drug-related pulmonary toxicity, diarrhea, colitis, uveitis or neurologic toxicity must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the BMS Medical Monitor.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor.

Dose delay/interruption of nivolumab which results in treatment interruption of > 8 weeks require treatment discontinuation, with exceptions as noted below.

Nivolumab Dose Discontinuation Due to Adverse Events

Nivolumab treatment should be permanently discontinued for the following reasons:

- Any Grade 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment

- Any Grade 3 non-skin, drug-related AE lasting > 7 days, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, myocarditis, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
- Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Grade ≥ 3 drug-related AST, ALT or Total Bilirubin requires discontinuation*
    - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2x ULN

  * In most cases of Grade 3 AST or ALT elevation, study treatment will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the BMS Medical Monitor/designee must occur.
- Any Grade 4 drug-related adverse event or laboratory abnormality (including but not limited to creatinine, AST, ALT, or Total Bilirubin), except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 drug-related endocrinopathy adverse events, such as, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor.
- Any event that leads to delay in dosing lasting > 8 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed. Prior to re-initiating treatment in a subject with a dosing delay lasting > 8 weeks from the previous dose, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed/interrupted. Periodic study visits to assess safety and laboratory studies should also continue as clinically indicated during such dosing delays/interruption.
  - Dosing delays lasting > 8 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor. Prior to re-initiating

treatment in a subject with a dosing delay lasting > 8 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed/interrupted. Periodic study visits to assess safety and laboratory studies should also continue as clinically indicated during such dosing delays/interruption.

- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.
- Immune-mediated adverse events as described in Appendix 5.

4.1.5.2 Daratumumab

In Cycles 1 to 2, daratumumab doses that fall outside of the pre-specified window of +3 days must be skipped.

In Cycle 3 through 6, daratumumab dosing may be delayed for up to 1 week. If unable to administer within 1 week, then the dose should be skipped and resumption of the daratumumab continues per the protocol defined schedule.

From Cycle 7 and beyond, daratumumab can be delayed within a 21-day window. Doses that fall outside the allowed window should be skipped.

Subjects experiencing a Grade 4 (life threatening) infusion reaction related to daratumumab must permanently discontinue daratumumab.

Daratumumab Dose Delays Due to AEs

On the first day of each new treatment cycle and before each daratumumab dose, the subject will be evaluated for possible toxicities that may have occurred after the previous dose(s). Dose modifications or delays will be made based on the toxicity experienced during the previous cycle of therapy or newly encountered on Day 1 of a cycle.

Daratumumab administration should be delayed if any of the following criteria below are met, to allow for recovery from toxicity related to the study drug:

- Grade 4 hematologic toxicity except for grade 4 lymphopenia
- Grade ≥ 3 thrombocytopenia
- Febrile neutropenia
- Neutropenia with infection, of any grade
- Grade ≥ 3 non-hematologic toxicities with the following exceptions:
  - Grade 3 nausea or Grade 3 vomiting that responds to antiemetic treatment within 7 days
  - Grade 3 diarrhea that responds to antidiarrheal treatment within 7 days
  - Grade 3 fatigue or asthenia that was present at baseline or that lasts for < 7 days after the last administration of daratumumab

If daratumumab administration does not commence within the prespecified windows of the scheduled administration date (Table 4.1.5.2-1), that respective dose should be skipped. Administration may resume at the next planned dosing date. A missed dose will not be made up.

Table 4.1.5.2-1: Daratumumab Windows of Dosing Resumption

Cycles	Dosing Frequency	Skip dose window	Dosing Resumption
1 and 2	Weekly (QW)	> 3 days	Next planned weekly dosing date
3 to 6	Biweekly (Q2W)	> 7 days	Next planned biweekly dosing date
7 and beyond	Every 4 weeks (Q4W)	> 21 days	Next planned every 4 weeks dosing date

Criteria to Resume Treatment with Daratumumab

Administration of daratumumab may be restarted upon recovery from toxicity to Grade 2 or baseline, with the exception that Grade 2 laryngeal edema or Grade 2 bronchospasm must be fully recovered.

Any adverse event deemed to be related to daratumumab that requires a dose hold of more than 4 weeks (Cycle 1 to Cycle 6) or more than 6 weeks (Cycle 7 and beyond) will result in permanent discontinuation of daratumumab.

In order to initiate a new infusion of daratumumab the following criteria must be met:

- Platelet count $\geq 50 \times 10^9$/L (platelet transfusion support is allowed)
- ANC $\geq 0.50 \times 10^9$/L (growth factor support is strongly recommended if ANC$< 1.0 \times 10^9$/L).

For subjects who have experienced HBV reactivation while on study treatment, if the benefits outweigh the risks, study treatment may be resumed with concomitant antiviral prophylaxis as per local standard of care.

Daratumumab Dose Discontinuation Due to Adverse Events

Daratumumab treatment should be permanently discontinued for the following reasons:

- Grade 4 infusion reaction related to daratumumab.
- The 3rd occurrence of a Grade 3 daratumumab infusion related reaction
- Subjects experiencing ≥ 8-week delay in all study drugs (nivolumab, daratumumab, pomalidomide, and dexamethasone) due to an AE(s) related to study treatment must be discontinued from all study treatment. Subjects experiencing delays unrelated to study therapy, for example due to radiation therapy, may delay study treatment up to 84 days. Further delays may be allowed after discussion with the BMS Medical Monitor.
- Any daratumumab related AE that requires a dose hold of > 4 weeks (Cycle 1 to Cycle 6) or > 6 weeks (Cycle 7 and beyond) will result in permanent discontinuation of daratumumab, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon.

4.1.5.3 Pomalidomide

Pomalidomide interruption should be performed as clinically indicated at the discretion of the investigator. Subjects should be instructed that if a dose of pomalidomide has been missed and it has been less than 12 hours since the subject's regular dosing time, to take pomalidomide as soon as the subject remembers. If it has been more than 12 hours, the dose must be skipped. Subjects should not take 2 doses at the same time.

In order to initiate a new cycle of pomalidomide, the following criteria must be met:

- Platelet count $\geq 50 \times 10^9$/L
- ANC $\geq 0.50 \times 10^9$/L (growth factor support is strongly recommended if ANC $< 1.0 \times 10^9$/L)
- Nonhematologic AEs must be resolved or improved as outlined in Section 4.1.6.

4.1.5.4 Dexamethasone

Dexamethasone interruption should be performed as clinically indicated at the discretion of the investigator. For subjects receiving daratumumab, the weekly dexamethasone that coincides with or is temporally closest to the next daratumumab dosing must be administered as part of the pre-infusion medication for daratumumab per the guidance in Section 4.1.4.2.

4.1.6 Recommended Dose Reductions for Nivolumab/Daratumumab Cohorts

The criteria presented in this section for dose modification of **dexamethasone** and **pomalidomide** are meant as general guidelines. They are based on current US standards of clinical practice. Local standards may differ and may be followed. Dose modification may occur in the setting of lower grade toxicity if the investigator, in consultation with the Medical Monitor/Sponsor, believes that it is in the interest of subject safety.

Dexamethasone

Dexamethasone dose reductions for toxicity must be performed as clinically indicated. Dose reductions and recommended management should follow the guidance in Table 4.1.6-1. Deviations to the recommended dose reductions are allowed based on the clinical judgment of the investigator.

Table 4.1.6-1: Dexamethasone Dose Reductions

CTCAE Category	Adverse Event	Treatment Adjustment
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1 - 2 (requiring medical management)	Treat with a proton pump inhibitor. If symptoms persist despite above measures, decrease by 1 dose level.
	≥ Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms are adequately controlled. Reduce by 1 dose level and resume along with concurrent therapy with a proton pump inhibitor. If symptoms persist despite above measures, reduce to dose level -3 (dose withheld).
	Acute pancreatitis	Reduce to dose level -3 (dose withheld).
Cardiovascular	Edema ≥ Grade 3 (limiting function and unresponsive to therapy or anasarca)	Use diuretics as needed, and decrease dexamethasone by 1 dose level. If edema persists despite above measures, decrease by another dose level.
Neurology	Confusion or Mood alteration ≥ Grade 2 (interfering with function ± interfering with activities of daily living)	Hold dexamethasone until symptoms resolve. Decrease by 1 dose level and resume. If symptoms persist despite above measures, decrease by another dose level.
Musculoskeletal	Muscle weakness ≥ Grade 2 (symptomatic and interfering with function ± interfering with activities of daily living)	Hold dose until muscle weakness is ≤ Grade 1. Decrease dexamethasone by 1 dose level and resume. If weakness persists despite above measures, decrease by another dose level.
Metabolic	Hyperglycemia ≥ Grade 3 or higher	Treat with insulin or oral hypoglycemics as needed. If uncontrolled despite above measures, decrease by 1 dose level until glucose levels are satisfactory.
Constitutional	Insomnia ≥ Grade 2	Decrease by 1 dose level and resume.

Dose reduction for persistent Grade 2 or Grade ≥ 3 AEs believed to be related to dexamethasone and not listed above are permitted.

On weeks with daratumumab infusion, regardless of dexamethasone dose reduction, at least 20 mg for subjects ≤ 75 years old or at least 16 mg for subjects > 75 years old of the weekly dexamethasone dose must be administered IV as part of the premedication for daratumumab with the remainder of the weekly dexamethasone dose administered orally (PO) post-infusion. Contact the Medical Monitor to discuss dexamethasone IV premedication for subjects who reach dose level -3 and must discontinue dexamethasone due to dose limiting toxicity.

On days without daratumumab, no IV dexamethasone should be administered (Table 4.1.6-2).

Table 4.1.6-2: Dexamethasone Dose Levels

Dose Level	Reducing Dexamethasone on Weeks with Daratumumab		Reducing Dexamethasone on Weeks Without Daratumumab	
	PO	IV	PO	IV
0	≤ 75 years old - 20 mg	20 mg	≤ 75 years old - 40 mg	N/A
	> 75 years old - 4 mg	16 mg	> 75 years old - 20 mg	
-1	≤ 75 years old - 12 mg	20 mg	≤ 75 years old - 20 mg	N/A
	> 75 years old - 2 mg	16 mg	> 75 years old - 12 mg	
-2	≤ 75 years old - 0 mg	20 mg	≤ 75 years old - 12 mg	N/A
	> 75 years old - 0 mg	16 mg	> 75 years old - 8 mg	
-3	≤ 75 years old - 0 mg	Contact Medical Monitor	≤ 75 years old - 0 mg	N/A
	> 75 years old - 0 mg		> 75 years old - 0 mg	

Pomalidomide

Below are the recommended dose adjustments for the management of thrombocytopenia and neutropenia judged by the investigator to be related to pomalidomide. Information in Table 4.1.6-3 and Table 4.1.6-4 is based on pomalidomide prescribing information, which contains additional guidance on pomalidomide dosing. Investigators should follow the guidelines in the prescribing information for pomalidomide.[104] Some clinically relevant events and their management are presented below.

Table 4.1.6-3: Treating Thrombocytopenia Related to Pomalidomide

When Platelet Count:	Recommended Course:
• Fall to < 25,000 per mm^3	• Interrupt pomalidomide treatment, follow Complete Blood Count weekly.
• Return to ≥ 50,000 per mm^3	• Resume pomalidomide at 3 mg daily
• For each subsequent drop < 25,000 mm^3	• Interrupt pomalidomide treatment
• Return to ≥ 50,000 mm^3	• Resume pomalidomide at 1 mg less than previous dose

Table 4.1.6-4: Treating Neutropenia Related to Pomalidomide

When Neutrophil Count:	Recommended Course:
• Fall to < 500 per mm^3 or febrile neutropenia (fever ≥ 38.5°C and ANC < 1,000 mm^3)	• Interrupt pomalidomide treatment, follow Complete Blood Count weekly.
• ANC returns to ≥ 1000 per mm^3	• Resume pomalidomide at 3 mg daily
• For each subsequent drop < 500 mm^3	• Interrupt pomalidomide treatment
• Return to ≥ 1000 mm^3	• Resume pomalidomide at 1 mg less than previous dose

ANC, absolute neutrophil count. In case of neutropenia, consider the use of growth factors in subject management.

If necessary to co-administer strong inhibitors of CYP1A2 in the presence of strong inhibitors of CYP3A4 and P-glycoprotein, consider reducing pomalidomide dose by 50%.[104]

4.1.7 Treatment During Follow-up

MM subjects in the nivolumab/daratumumab cohorts will receive treatment until disease progression and will not be eligible for additional study therapy after confirmation of disease progression.

4.2 Method of Assigning Subject Identification

After informed consent has been obtained, the subject must be enrolled into the study by calling an interactive voice response system (IVRS) to obtain the subject number. The exact procedure for using the IVRS will be detailed in a separate document.

4.3 Blinding/Unblinding

Not applicable.

4.4 Treatment Compliance

Study drug will be administered in the clinical facility. The investigator or their designated study personnel will maintain a log (Drug Accountability Log) of all study drugs received dispensed and destroyed. The investigator and the study personnel will ensure that each subject receives the calculated dose of the study drug based on body weight.

Drug supplies will be inventoried and accounted for throughout the study. The Drug Accountability Log will be reviewed by the study monitor during site visits and at the completion of the study. Any discrepancy should be brought to the attention of the Sponsor.

4.5 Destruction and Return of Study Drug

4.5.1 Destruction of Study Drug

For this study, study drugs (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials and syringes may be destroyed on site.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible BMS Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.

- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met the responsible BMS Study Monitor will make arrangements for return of study drug.

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

4.5.2 Return of Study Drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible BMS Study Monitor.

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

[redacted]

5.2 Study Materials

- Instructions and kits for collections, processing and shipment of blood and tissue samples
- Investigator Brochure
- Local laboratory data entry instructions
- IVRS registration instructions
- Study drug supplies
- CRF Instructions
- SAE forms
- Pregnancy Surveillance Forms
- CTCAE version 4.0.

5.3 Safety Assessments

Adverse events will be assessed continuously during the study and for 100 days post last treatment. Adverse events will be coded using the most current version of MedDRA and reviewed for potential significance and clinical importance. Adverse events will be evaluated according to the NCI CTCAE Version 4.0 dated June 14, 2010. Subjects should be followed until all treatment-related AEs have recovered to baseline or are deemed irreversible by the investigator.

Only data for the procedures and assessments specified in this protocol should be submitted to BMS. Additional procedures and assessments may be performed as part of standard of care; however, the data for these assessments should remain in the subject's medical record and should not be provided to BMS, unless specifically requested from the Sponsor. Safety assessments must be done prior to dosing. The local safety labs (complete blood count, chemistry panel) and procedures may be collected or performed up to 3 days prior to the visit. For subjects who skip a dose, local safety labs results must be collected at least once per cycle.

All subjects will be assessed for safety. Safety evaluations include assessments of AEs, clinical laboratory tests (hematology, chemistry), vital sign measurements, and physical examination with assessment of ECOG PS. Investigators are responsible for monitoring the safety of subjects who have entered this study and for alerting the Sponsor to any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject. The investigator is responsible for appropriate medical care of subjects during the study.

5.3.1 Laboratory Assessments

Laboratory assessments for safety will be performed at local laboratories. Safety laboratory assessments are listed in the Flow Chart/Time and Events Schedule presented in Section 5.1.

5.4 Efficacy Assessments

Efficacy assessment will be conducted and reported on the eCRF using the appropriate efficacy assessment based on tumor type. Subjects with multiple myeloma will be evaluated with the International Myeloma Working Group Uniform Response Criteria to define response and progressive disease (Appendix 3).

5.4.1 Efficacy Assessments in the Nivolumab/Daratumumab Cohorts

Efficacy endpoints in MM subjects in the nivolumab/daratumumab cohorts will be based on analysis of molecular and cytometry minimal residual disease (MRD) and based on serum and urine electrophoresis (SPEP and UPEP) with immunofixation, sFLC (for those with sFLC only disease), corrected calcium (serum calcium and serum albumin), imaging and bone marrow assessments, all at predefined intervals as specified in Section 5.1.

Assessments done at local laboratories versus central laboratories are indicated in Section 5.1. Assessments for molecular and cytometry MRD, and of SPEP, UPEP and sFLC will be based on central lab results, whereas assessments of bone lesions, extramedullary plasmacytomas, bone marrow disease assessment and corrected calcium will be based on local analysis at the site. Efficacy assessments in subjects in the nivolumab-daratumumab Cohort A will be performed at the respective local laboratory.

5.4.1.1 Primary Efficacy Assessment: MRD

Molecular minimum residual disease (MRD) assessment will be performed via the Adaptive® ClonoSIGHT assay and bone marrow aspirate samples are required at the following time points:

- Bone marrow aspirate samples at Screening, Day 1 Cycle 4 or at the time of VGPR or better, whichever occurs first, and every 6 cycles thereafter until disease progression. In subjects with confirmed PD prior to Day 1 Cycle 4, bone marrow aspirate will be performed upon confirmation of PD. If bone marrow aspirate was inadvertently not collected or unable to be collected at these required time points, the study medical Monitor should be contacted to discuss the timing of the collection

Cytometry MRD from bone marrow aspirates will be done at the same time points as for molecular MRD, except for the Screening timepoint.

5.4.1.2 Secondary Efficacy Assessment: IMWG Response

Modified IMWG Response criteria in Appendix 3 will be used for the efficacy analysis. All response and progression categories require 2 consecutive assessments to confirm response and progression before initiation of any new therapy. For the purposes of this study, all subjects' tumor assessments by myeloma laboratory tests (SPEP M protein and UPEP M protein quantification, corrected calcium (calcium and albumin), and serum free light chain) should be re-evaluated per the protocol-stated frequency relative to the date of first dose of study drug until disease progression based on Appendix 3, irrespective of dose delays or treatment cycle. **If subject does not have documented disease progression as defined in Appendix 3 at the time**

of study drug discontinuation, then tumor assessments must continue to be performed according to the same schedule described above until disease progression even if a subsequent anti-myeloma treatment is initiated prior to disease progression. Subjects will be followed every 12 weeks, or more frequently, after disease progression for survival, subsequent myeloma therapy, and, for subjects treated with pomalidomide, development of second primary malignancy.

All efficacy laboratory assessments (SPEP, UPEP, serum/urine immunofixation, and sFLC) should be done through the central laboratory for subjects in Cohort B, except for corrected calcium (serum calcium and serum albumin) which will be done locally. Bone marrow assessments for plasma cell percentage and light chain restriction (clonality by IHC or flow cytometry) will be done locally per institution standard practice. For any SPEP, UPEP, or sFLC assessment performed locally, in lieu of a central laboratory assessment, (ie, if the subject cannot complete a visit at the study site), M protein absolute quantification (eg, g/dL or mg/24 hrs) in serum and urine or sFLC (eg, mg/L or mg/dL) must be performed. Any laboratory samples analyzed locally, including for efficacy, must be entered on the appropriate CRF/eCRF as requested by the Sponsor to properly assess efficacy per protocol criteria.

Subjects in Cohort A will have all efficacy assessments performed at the local laboratory.

Laboratory Assessments for Multiple Myeloma

All laboratory efficacy assessments must be performed until disease progression or withdrawal of consent, even if the subject is discontinued from study therapy and has started new myeloma therapy. Confirmation of ≥ PR or PD is required on 2 consecutive assessments for serum, urine and sFLC.

Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both, the serum protein electrophoresis (SPEP) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and of disease progression by International Myeloma Working Group (IMWG) criteria in some patients with IgG kappa myeloma protein.

It is likely that nivolumab may also be detected by SPEP and immunofixation but this is still under investigation. Serum or peripheral blood samples collected during the study may be analyzed for the presence of monoclonal antibody interference with endogenous patient M protein quantification.

1) **Serum**: SPEP for M protein quantification, total serum protein, serum immunofixation, and quantitative immunoglobulin assay.
   a. Serum Immunofixation (IFE) is required at baseline and to confirm CR regardless of whether measurable M-protein was present at baseline.
   b. Subjects with measurable disease in SPEP will be assessed for response based on SPEP and not by the serum FLC assay.
   c. Subjects with measurable disease in both SPEP and UPEP will be assessed for response based on these two tests and not by the serum FLC assay.

d. Subjects with FLC only disease should be monitored by sFLC only

2) Serum free light chain (sFLC):
   a. Subjects without measurable serum M-protein (ie, < 0.5 g/dL [5 g/L]) or urine M-protein (ie, < 200 mg [0.2 g] per 24 hours) and considered oligosecretory must have sFLC assessed at each cycle until progression.
   b. SPEP and UPEP must be monitored at all time points in oligosecretory patients for potential disease progression determination.
   c. Serum for sFLC must be collected at time of serum and urine IFE negativity to confirm sCR in all subjects.
3) **Urine**: 24-hour urine collection for M protein quantification and immunofixation. 24-hour urine must be collected with each cycle for all subjects.
   a. Urine Immunofixation (IFE) is required at baseline and to confirm CR, regardless of whether measurable M-protein was present at baseline.
   b. Subjects with measurable disease in UPEP will be assessed for response based on UPEP and not by the serum FLC assay.
4) **Bone marrow aspiration/biopsy** (Section 5.6.1.1):
   a. **Bone marrow aspirate for evaluation of percentage plasma cells and light chain restriction:** samples are required at Cycle 4 Day 1 or at the time of VGPR or better, whichever occurs first, and then every 6 cycles thereafter until PD (second bone marrow sample not required for confirmation). See Section 5.4.1.1.
   b. **Bone marrow biopsy** is not required by protocol unless an aspirate sample (at any timepoint above) is not available due to a dry tap.

Table 5.4.1.2-1: Bone Marrow Samples

Sample	Local Laboratory	Central Laboratory
Aspirate	Samples are required at the following times: • Screening (plasma cell percentage only) • C4D1 or ≥ VGPR, whichever occurs first, then every 6 cycles until progression • In subjects with progression before C4D1, bone marrow aspirate should be done upon progression confirmation. Evaluation of plasma cell percentage and light chain restriction assessments (clonality by IHC or flow cytometry) performed locally per institution standard practice	Genetic assessments (FISH): samples are required at screening Biomarker assessments: samples are required at • Screening • C4D1 or ≥ VGPR, whichever occurs first, then every 6 cycles until progression • In subjects with progression before C4D1, bone marrow aspirate should be done upon progression confirmation
Biopsy	Not required by protocol unless an aspirate sample (at any time point above) is not available due to a dry tap	NA

Genetic assessments (FISH) should be performed by the central laboratory on a fresh bone marrow sample. However, if a new bone marrow sample collection is not feasible and if this assessment was performed locally during the screening period, the local results must be entered into the eCRF. Contact BMS medical monitor in these cases.

5) **Serum Corrected Calcium**: Serum corrected calcium should be collected with each cycle for all subjects until disease progression.

Corrected Calcium, mg/dL = (0.8 x [Normal Albumin, g/dL - Subject's Albumin, g/dL] + Serum Ca, mg/dL

Imaging Assessments for Myeloma

Skeletal Survey

Skeletal survey, by conventional radiography, for metastatic disease will be performed within 28 days of randomization in all subjects. Skeletal survey will be performed on study if clinically indicated (development of compression fracture does not exclude response). Use of conventional or low dose CT scan (ie, of the spine) or PET/CT bone survey is acceptable. If imaging is performed on treatment for assessment of progression, the site must use the same modality of imaging as used in screening. The number and location of skeletal lesions and whether they are lytic should be recorded on the eCRF. On-treatment survey should record whether there is an increase in the number or size of lytic lesions.

Assessment of Extramedullary Plasmacytoma

Computed tomography or MRI should be performed at screening, if clinically indicated or if patient had a previous extramedullary or bone plasmacytoma. To minimize unnecessary radiation in myeloma subjects where progression is primarily based on serum and urine M-protein, on study assessments should only be performed if clinically indicated (i.e., pain, concern for disease progression), whether or not present at baseline, and at the time of CR/sCR assessment.

A sum of the products of the longest diameters and longest perpendicular diameter for all measurable lesions will be calculated at screening. This sum will be used as the reference for on study assessments by which to characterize the objective tumor response.

All tumor measurements must be made in millimeters. All documented measurable and non-measurable lesions are to be followed throughout the trial. All assessments to be used for tumor response evaluation, including the baseline assessment, must be performed using the same method for repeat assessment. CT and MRI scanning are the preferable methods of assessment. Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less or with cuts of 5 (or 10) mm if spiral CT scanning is used. Imaging-based evaluation is preferred to evaluation by clinical examination. Evaluation by chest x-ray is less preferable than CT or MRI, and should only be used for well-defined lesions surrounded by aerated lung. Clinical examination is only acceptable when lesions are superficial, such as a skin nodule or palpable lymph node. Skin lesions must be documented by a photograph with a ruler. Ultrasound is not acceptable for documentation of measurable disease.

For patients with MM, duplicate copies of all imaging studies used for tumor response evaluation will be made available for review by the Sponsor upon request.

Measurable disease are lesions that can be accurately measured in 2 dimensions and both diameters must be ≥ 20 mm when evaluated by standard CT scanning or ≥ 10 mm when evaluated by spiral CT scanning or MRI. The minimum diameter size should be at least twice the slice thickness.

Non-measurable disease are all other lesions (or sites of disease), including those that are too small (ie, do not meet above criteria), occur within a previously irradiated area (unless they are documented as new lesions since the completion of radiation therapy), bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusion (exception for effusions documented by cytology as not malignant or present at baseline without progression), lymphangitis cutis/pulmonis, abdominal masses that are not pathologically/cytologically confirmed and followed by imaging techniques, and cystic lesions.

5.4.2 Bone Marrow Biopsy and Aspiration

Bone marrow aspirates will be mandated for all subjects for biomarker assessments at screening, C4D1 or ≥ VGPR, whichever occurs first, then every 6 cycles until progression. In subjects with progression before C4D1, bone marrow aspirate should be done upon progression confirmation.

Nivolumab/Daratumumab Cohorts

Bone marrow aspirates will be required in all subjects in these cohorts. Bone marrow biopsy is optional. Bone marrow biopsy is required if an aspirate sample (at any required time point) is not available due to a dry tap.

At the time of the scheduled bone marrow aspirate, the PI will determine if there have been significant changes in the clinical course to suggest that subjects can no longer undergo the procedure safely. These subjects for whom the PI finds the degree of risk associated with the procedure not acceptable may continue therapy.

The first aspirate will be obtained prior to therapy (within 28 days). The next aspirates must be obtained at Day 1 Cycle 4 or at the time of VGPR or better, whichever occurs first, and then every 6 cycles until disease progression.

At the time of disease progression or end of treatment, bone marrow aspirate collections are optional but strongly encouraged to investigate the mechanisms of resistance to the therapy (See Section 5.6.1.1). See Table 5.1-6 for collection time points.

In subjects with confirmed PD prior to Day 1 Cycle 4, bone marrow aspirate must be obtained upon confirmation of PD.

Bone marrow biopsies are not required by protocol unless an aspirate sample (at any time point in Table 5.1-6) is not available due to a dry tap and can be used only for disease assessment.

5.5 Pharmacokinetic Assessments

5.5.1 Pharmacokinetic Collection & Processing

Table 5.1-7 lists the PK sampling schedule to be followed in the daratumumab combination cohorts. Cmin will be reported for all subjects with available data for the assessment of PK. Cmin and concentrations at end-of-infusion will be reported for all subjects with available data for the assessment of PK. Serial samples will be collected after the first dose and at additional time points. All on-treatment predose and end-of-infusion PK time points are intended to align with days on which study drug is administered. If dosing occurs on a different day, the PK sampling should be adjusted accordingly. Further details of sample collection, processing, and shipment are provided in the laboratory manual.

5.5.2 Pharmacokinetic Sample Analyses

The serum samples will be analyzed for nivolumab by validated methods. In addition, selected serum samples may be analyzed by an exploratory analytical method that measures nivolumab and/or daratumumab for technology exploration purposes; exploratory results will not be reported.

[redacted]

[redacted]

5.10 Results of Central Assessments

All myeloma efficacy laboratory assessments in Cohort B should be performed by the central laboratory. Investigative site staff will receive reports of the results on an ongoing basis for treatment decisions and patient management throughout the study. Any laboratory samples analyzed locally, including those for efficacy, must be entered on the appropriate CRF/eCRF as requested by the Sponsor to properly assess efficacy per protocol criteria.

6 ADVERSE EVENTS

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

The causal relationship to study drug is determined by a physician and should be used to assess all AEs. The casual relationship can be one of the following:

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

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

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

6.1 Serious Adverse Events

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

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

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

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

NOTE:

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

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

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the nivolumab IB represent the Reference Safety Information to determine expectedness of SAEs for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 100 days of discontinuation of dosing or within 30 days of the last visit for screen failures. For subjects randomized but never treated with any study drug, SAEs should be collected for 30 days from the date of randomization.

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). When using paper forms, the reports are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: See Contact Information list.

SAE Facsimile Number: See Contact Information list.

For studies capturing SAEs/pregnancies through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted

immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

SAE Telephone Contact (required for SAE and pregnancy reporting): See Contact Information list.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term[s] initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

A SUSAR (Suspected, Unexpected Serious Adverse Reaction) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

6.2 Nonserious Adverse Events

A ***nonserious adverse event*** is an AE not classified as serious.

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects. All non-serious AEs (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study drug treatment.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

6.4 Pregnancy

If, following initiation of the investigational product, it is discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least time to washout plus one ovulatory cycle (30 days) for a total of 23 weeks, or plus one spermatogenesis cycle (90 days) for a total of 31 weeks after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures.

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information, must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 Overdose

An overdose is defined as accidental or intentional administration of any dose of product that is considered both excessive and medically important. All occurrences of overdose must be reported as SAEs (see Section 6.1.1 for reporting details).

6.6 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1 for reporting details).

Potential drug induced liver injury is defined as

1) AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

3) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

Second primary malignancies (SPMs) will be collected throughout the study for subjects treated with pomalidomide and includes assessments during survival follow-up. All SPMs that occur during the screening period and within 100 days of discontinuation of dosing will be reported as an SAE regardless of relationship to study drug. Additionally, any SPM that occurs after this timeframe and considered related to study drug will be reported as an SAE. All other SPMs will be collected and reported on a separate CRF page.

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

Not applicable.

8 STATISTICAL CONSIDERATIONS

[redacted]

8.2 Populations for Analyses

- All Enrolled Subjects: All subjects who sign informed consent form and were registered in IVRS.
- All Treated Subjects: All subjects who receive at least one dose of nivolumab and/or daratumumab.
- Response Evaluable Subjects: All treated subjects with measurable disease at baseline and one of the following: 1) at least one on-treatment efficacy assessment, 2) clinical progression, or 3) death.
- Pharmacokinetic (PK) Subjects: All subjects who receive at least one dose of study medication and have available serum concentration data.
- Biomarker Subjects: All subjects who receive at least one dose of study medication and have available biomarker data
- Immunogenicity Subjects: All subjects who receive at least one dose of study medication and have available ADA data.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

8.3.1.1 Safety

The primary objective relates to evaluate the safety and tolerability of the nivolumab and daratumumab combination therapy in subjects with relapsed/refractory MM. This objective will be measured by the following endpoints:

- Number and percent of subjects that experience drug-related grade 3-4 AEs occurring up to 100 days after the last dose of study drug. [Time Frame - On a continuous basis up to 100 days after the last dose of study drug];
- Number and percent of subjects that experience drug-related grade 3-4 SAEs occurring up to 100 days after the last dose of study drug. [Time Frame - On a continuous basis up to 100 days after the last dose of study drug];
- Number and percent of subjects with clinical laboratory abnormalities by worst toxicity grade by NCI CTCAE version 4.0 (as assessed at the planned times listed in Section 5.1). (Time Frame - On a continuous basis up to 100 days after the last dose of study drug).

8.3.2 Secondary Endpoint(s)

8.3.2.1 Efficacy

The secondary objective relating to efficacy is to assess the preliminary antitumor activity in the combination of nivolumab and daratumumab in subjects with relapsed/refractory MM. This objective will be measured by minimal residual disease status (MRD), objective response rate (ORR), duration of response (DOR), and progression-free survival (PFS) for MM subjects in each treatment regimen group.

Minimal Residual Disease (MRD) in the Nivolumab/Daratumumab Cohorts

Both cytometry and molecular MRD from bone marrow aspirate will be evaluated.

The time point for MRD negative status for MM subjects in the nivolumab/daratumumab cohorts is a dichotomized variable for quantifiable MRD detection.

The first MRD negativity status is defined as the first negative status designation over the study as a whole, recorded between the date of first dose and the last efficacy assessment prior to subsequent therapy.

The best MRD negativity status is defined as the best status designation with the minimum MRD levels over the study as a whole, recorded between the date of first dose and the last efficacy assessment prior to subsequent therapy.

Objective Response Rate (ORR)

Best overall response (BOR) is defined as the best response designation over the study as a whole, recorded between the date of first dose and the last efficacy assessment prior to subsequent therapy.

Objective response rate is defined as the proportion of subjects who had a BOR of either partial response (PR) or complete response (CR) divided by the number of treated subjects (or response-evaluable subjects).

Duration of Objective Response (DOR)

The duration of response is defined as the time when the measurement criteria are first met for objective response until the date of documented disease progression or death, whichever occurs first. For subjects who neither progress nor die, the duration of response will be censored at the date of their last disease assessment.

Progression Free Survival (PFS)

Progression free survival (PFS) is defined as the time between date of randomization and date of progression or death, whichever occurs first. Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last efficacy assessment. Subjects who did not have any on study efficacy assessments will be censored on the date of randomization.

8.3.2.2 Pharmacokinetic

The following pharmacokinetic parameters of nivolumab will be derived from serum concentration time profiles for all subjects and subjects following the full PK profile sampling schedule in the combination cohorts. Cmin and Ceoinf will be reported for all subjects with available data. These parameters are used to measure the secondary objective related to pharmacokinetics.

Cmax - Maximum observed serum concentration

Tmax - Time of maximum observed serum concentration

In addition, the following parameters will be determined for all subjects:

Cmin - Serum concentration achieved at the end of dosing interval (trough concentration, all subjects)

AUC(0-T) -Area under the plasma concentration-time curve from time zero to the last time of the last quantifiable concentration.

AUC(TAU) - Area under the concentration-time curve in one dosing interval

Ceoinf - Serum concentration achieved at the end of study drug infusion

8.3.2.3 Immunogenicity

The secondary objective relating to immunogenicity will be measured by the ADA status both at the sample level and at the subject level. At the sample level a sample is characterized as baseline ADA-positive, ADA-positive or ADA-negative to each study drug. At the subject level, relevant ADA endpoints include proportion of subjects with a Baseline ADA-positive sample, and proportion of ADA-positive subjects for each study drug. Time points for collection are specified in Table 5.1-7. Additional details will be presented in the SAP.

[redacted]

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Subject demographics and baseline characteristics including age, sex, race, ethnicity, weight, baseline disease diagnosis, and medical conditions will be summarized by treatment group and overall using descriptive statistics.

8.4.2 Efficacy Analyses

MRD negativity status for MM subjects in the nivolumab/daratumumab cohorts will be evaluated by time points. The frequency of the MRD negativity status and the best MRD negativity status will be summarized by treatment group. The cross tabulation of the MRD negativity status and BOR will be presented. Summary statistics of the MRD levels and their corresponding percent changes from baseline will be tabulated by planned study day by treatment group. Potential association between the first/best MRD negativity status with PFS and OS may be evaluated as appropriate. Additional details will be presented in the Statistical Analysis Plan.

Individual best overall response (BOR), duration of response and PFS will be listed, using the IMWG Uniform Response Criteria for Multiple Myeloma.[106]

BOR outcomes will be tabulated by treatment group. The objective response rate (ORR) and corresponding 95% exact CI will be provided by treatment group. The median duration of response and PFS and corresponding two-sided 95% CIs will be estimated by Kaplan-Meier methodology. The analysis of overall survival would be exploratory. Kaplan-Meier plots of PFS, DOR, and OS will be provided.

Final analysis will be performed after all treated subjects have been followed for a minimum of 3 months to evaluate the efficacy endpoints.

8.4.3 Safety Analyses

All recorded AEs will be listed and tabulated by system organ class, preferred term, and dose and coded according to the most current version of MedDRA

All recorded AEs will be listed and tabulated by system organ class, preferred term, treatment, dose and coded according to the most current version of MedDRA across disease types. A subset of adverse event tables may be summarized by disease type. DLTs will be described by treatment and dose. The incidence of AEs will be reviewed for potential significance and clinical importance. AEs will be coded according to the most current version of MedDRA. Vital signs and clinical laboratory test results will be listed and summarized by treatment and dose. Any significant physical examination findings and results of clinical laboratory tests will be listed. ECG results will be evaluated by the investigator and abnormalities, if present, will be listed.

8.4.4 Pharmacokinetic Analyses

Summary statistics will be tabulated for the pharmacokinetic parameters of nivolumab in the presence of daratumumab by treatment, disease type, dose and study week as appropriate for all subjects receiving nivolumab monotherapy and subjects following the full PK profile sampling schedule in the combination cohorts. Cmin will be summarized for all subjects. To describe the dependency on dose, scatter plots of Cmax and AUC(0-T) versus dose will be provided for each day measured by treatment and study drug. To assess attainment of steady state, plots of Cmin versus time will be provided by treatment and by study drug for all subjects. Pharmacokinetic concentrations of nivolumab from all subjects will be listed, and may be used in combination

with other studies for exposure-response or population PK modeling, which will be part of a separate report.

[redacted]

8.4.7 Other Analyses

8.4.7.1 Immunogenicity

A listing will be provided of all available immunogenicity data. Additionally, a listing of immunogenicity data from those ADA positive subjects will be provided. The frequency of baseline positive subjects, and frequency of ADA positive subjects will be provided by treatment group. The frequency of neutralizing antibodies will be provided based on data availability. To examine the potential relationship between immunogenicity and safety, the frequency and type of AEs of special interest may be examined by overall immunogenicity status. Associations between pre-dose concentrations of nivolumab, biomarkers, efficacy, and corresponding ADA assessments may be explored. Additional details will be provided in the SAP.

8.5 Interim Analyses

Administrative interim analyses may be performed as needed prior to completion of the study in order to facilitate program decisions and to support presentations or publications.

In addition to the administrative interim analyses over the course of the study, safety and/or efficacy updates may also be performed according to health authority requests.

8.5.1 Nivolumab Daratumumab Cohort B

An interim analysis to evaluate preliminary safety and efficacy is scheduled for Cohort B when 50% of treated patients from each treatment arm (ND and D) have had a minimum of 3 months of follow-up.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- BMS
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

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

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.

9.1.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to BMS.

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of investigational product (those supplied by BMS) is maintained at each study site where study drug and are inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- nonstudy disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to BMS
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

BMS will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained.

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paper or electronic SAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected considering the following criteria: Subject recruitment (eg, among the top quartile of enrollers)

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study require approval by BMS prior to publication or presentation and must adhere to BMS's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to BMS at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in

the CTA. BMS shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

10 GLOSSARY OF TERMS

Term	Definition
Adverse Reaction	An adverse event that is considered by either the investigator or BMS as related to the investigational product
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator Brochure for an unapproved investigational product)

11 LIST OF ABBREVIATIONS

ABO	Antibodies blood group
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferace
BM	Bone marrow
BMSC	Bone marrow stromal cells
BOR	Best overall response
BORR	Best overall response rate
BP	Blood pressure
CDC	Complement-dependent cytotoxicity
CI	Confidence interval
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridization
FSH	Follicle stimulating hormone
GCP	Good clinical practices
GCSF	Granulocyte colony stimulating factor
HBV SAg	Hepatitis B-virus surface antigen
HCV RNA	Hepatitis C virus ribonucleic acid
HIPAA	Health Information Portability and Accountability Act
HL	Hodgkin lymphoma
HLA	Human leukocyte antigen
HSCT	Hematopoietic stem cell transplant
ICF	Informed Consent Form
IEC	Independent Ethics Committee
iMiD	Immune modulatory drug
IP	Investigational product
IRB	Institutional Review Board
ITIM	Immunoreceptor tyrosine inhibitory motif

ITSM	Immunoreceptor tyrosine-based switch motif
IV	Intravenous
KIR	Killer immunoglobulin-like receptor
LFTs	Liver function tests
mAb	Monoclonal antibody
MDSC	Myeloid-derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major histocompatibility complex
MM	Multiple myeloma
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
MTD	Maximum-tolerated dose
NK	Natural killer
NSCLC	Non small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed death-1
PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2
PET	Positron emission tomography
PFS	Progression free survival
PMBL	Primary mediastinal B cell Lymphoma
PO	By mouth
PPK	Population pharmacokinetics
PR	Partial response
RCC	Renal cell carcinoma
SAE	Serious adverse event
SD	Stable disease
TCR	T-cell receptor
TTP	Time to progression
ULN	Upper limit of normal
US	United States
(USPI)	United States prescribing information
VGPR	Very good partial response
WOCBP	Women of child bearing potential

Protocol Number: CA209039
IND Number: 124,055
EUDRACT Number N/A
Date: 13-Mar-2012
Revised Date: 01-Oct-2015

Clinical Protocol CA209039

A Phase I Dose Escalation Study to Investigate the Safety, Pharmacokinetics, Immunoregulatory Activity, and Preliminary Antitumor Activity of Anti-Programmed-Death 1 (PD-1) Antibody (Nivolumab, BMS936558) and the Combinations of Nivolumab and Ipilimumab or Nivolumab and Lirilumab in Subjects with Relapsed or Refractory Hematologic Malignancy

Revised Protocol Number: 10
Incorporates Amendment: 11

Study Director/Central Medical Monitor
M.Brigid Bradley-Garelik, MD, MPH

Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 10	01-Oct-2015	Incorporates Amendment 11
Amendment 11	01-Oct-2015	Update follow up requirements
Revised Protocol 09	15-Apr-2015	Incorporates Amendment 10
Amendment 10	15-Apr-2015	Retrospectively collect radiographic images for blinded independent central review
Revised Protocol 08	05-Feb-2015	Incorporates Amendment 09
Amendment 09	05-Feb-2015	Removes exploratory cohorts from the nivolumab/ipilimumab cohorts
Revised Protocol 07	02-Dec-2014	Incorporates Amendment 08
Amendment 08	02-Dec-2014	Revises protocol to meet FDA guidance.
Revised Protocol 06	20-Aug-2014	Incorporates Amendment 07
Amendment 07	20-Aug-2014	Adds an additional set of cohorts (approximately 80 additional subjects) for dose expansion with combination of lirilumab and nivolumab
Revised Protocol 05	19-Dec-2013	Incorporates Amendment 06
Amendment 06	19-Dec-2013	Adds an additional set of cohorts (approximately 75 additional subjects) for dose escalation and dose expansion with combination of ipilimumab and nivolumab.
Revised Protocol 04	10-Oct-2013	Incorporates Amendment 05
Amendment 05	10-Oct-2013	Includes corrections for protocol clarity.
Revised Protocol 03	25-Jun-2013	Incorporates Amendment 04
Amendment 04	25-Jun-2013	Eliminate the CML cohort in the expansion phase as recruitment would be difficult due to lack of concomitant therapy with a tyrosine kinase inhibitor and increase the size of the remaining four cohorts from 16 to 23 subjects to redistribute the allotted patients from the eliminated CML cohort.
Revised Protocol 02	06-Mar-2013	Incorporates Amendment 03
Amendment 03	06-Mar-2013	Inclusion of non-clinical safety findings related to reproductive toxicology data
Revised Protocol 01	21-Dec-2012	Incorporates Administrative Letter 01 and Amendment 02
Amendment 02	21-Dec-2012	Eliminate the highest (10 mg/kg) of three dose levels scheduled to be examined, require that 8 of 16 subjects with multiple myeloma be required to undergo bone marrow biopsy while on therapy, and modify the discontinuation criteria to be more stringent
Administrative Letter 01	23-May-2012	Update Medical Monitor
Original Protocol	13-Mar-2012	Not applicable

SYNOPSIS

Clinical Protocol CA209039

Protocol Title: A Phase I Dose Escalation Study to Investigate the Safety, Pharmacokinetics, Immunoregulatory Activity, and Preliminary Antitumor Activity of Anti-Programmed-Death 1 (PD-1) Antibody (Nivolumab, BMS936558) and the Combinations of Nivolumab and Ipilimumab or Nivolumab and Lirilumab in Subjects with Relapsed or Refractory Hematologic Malignancy

For the combinations of nivolumab and ipilimumab or nivolumab and lirilumab administered concurrently, data will be compared to that obtained from subjects who were enrolled previously in the nivolumab monotherapy portion of this study.

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Intravenous (IV) infusion of BMS-936558 (nivolumab) at doses of 1 mg/kg or 3 mg/kg. The first dose will be followed by a 3 week evaluation period for pharmacokinetics and pharmacodynamics at the tumor site. Subsequent doses will be given at 2 week intervals. Doses should be administered over a 1-hour period. Therapy will be continued for up to 2 years with the potential for one additional year of therapy for retreatment eligible subjects in follow up.

Study Phase: 1

Research Hypothesis: The purpose of this study is to evaluate the safety profile and tolerability following administration of nivolumab in subjects with relapsed or refractory hematologic malignancy and specifically to indentify dose limiting toxicities (DLT's), particularly hematologic toxicities and the maximum tolerated dose (MTD), up to 3 mg/kg, in subjects with hematologic compromise.

Objective(s):

Primary Objective: To establish the dose limiting toxicities, maximum tolerated dose and recommended phase 2 dose for nivolumab up to a maximum of 3 mg/kg administered every 2 weeks to subjects with relapsed/refractory hematologic malignancy.

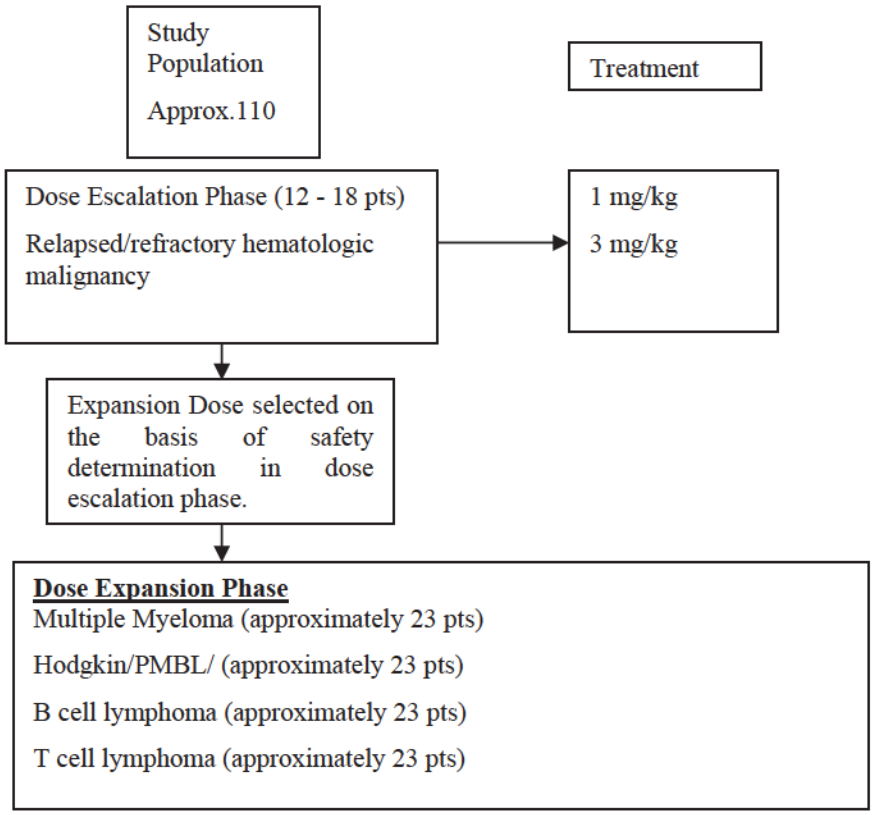
Secondary Objectives:

- To characterize the pharmacokinetics of nivolumab
- To assess the preliminary antitumor activity of various dose levels of nivolumab in subjects with relapsed/refractory hematologic malignancy
- To characterize the immunogenicity of nivolumab
- To assess the potential association between PD-L1 expression on tumor cells by immunohistochemistry and clinical efficacy measures

[redacted]

Study Design: Subjects will receive study drug as detailed in Figure 1.

Figure 1: **Study Design**



Study Population: Subjects with the following relapsed or refractory tumors: B cell lymphoma particularly, primary mediastinal B cell Lymphoma (PMBL), T cell lymphoma, Multiple Myeloma (MM), Hodgkin Lymphoma (HL), or Chronic Leukemias are eligible. Granulocyte count must be > 1000/μL and platelet count > 50,000/μL. Subjects with myelodysplasia, polycythemia vera, idiopathic thrombocythemia, myelofibrosis, acute leukemias, blast phase CML, T cell lymphoblastic or Burkitt lymphoma are excluded. Subjects with autoimmune disorders are excluded.

Study Assessments:

Safety Evaluation: Adverse events will be assessed continuously during the study and for 100 days post last treatment. Adverse events will be coded using the most current version of MedDRA and reviewed for potential significance and importance. Adverse events will be evaluated according to the NCI CTCAE Version 4.0. Subjects should be followed until all treatment-related adverse events have recovered to baseline or are deemed irreversible by the investigator.

Pharmacokinetic Evaluation: Serial blood samples for pharmacokinetic assessments will be collected from all subjects at specified time points.

Efficacy Evaluation: Subjects with non-Hodgkin's lymphoma or Hodgkin lymphoma will be evaluated using the International Workshop to Standardize Response Criteria for non-Hodgkin's Lymphomas (Appendix 1), subjects with multiple myeloma with the International Myeloma Working Group Uniform Response Criteria to define response and progressive disease (Appendix 3), subjects with CML with the CML criteria for evaluation (Appendix 2), and subjects with cutaneous T cell Lymphoma with the Clinical End Points and Response Criteria in Mycosis Fungoides and Sezary Syndrome. Radiographic images may be collected for blinded independent central review.

[redacted]

Statistical Considerations:

Sample Size: The sample size in the escalation phase is not based on statistical consideration, but rather depends on the number of observed toxicities; between 6 and 9 subjects are expected to be treated at each dose. At the dose expansion cohorts, approximately 23 subjects are expected to be enrolled in each of four tumor types and treated at the previously determined MTD or if no MTD is identified a maximum dose of 3 mg/kg.

In an expansion cohort, if 4 (17.4%) or 5 (21.7%) responses are observed with 23 subjects in each cohort, then the lower limit of the 90% one-sided confidence intervals for the objective response rate would be 7.8% and 11.0% respectively. These calculations are based on the Clopper-Pearson method for exact confidence intervals.

In addition, if the true ORR in a tumor type/expansion cohort is 20% then with 23 patients in each cohort there is 86.7% chance of observing at least 3 responses or 13.3% chance of observing 0, 1 or 2 responses (false negative rate). If the true ORR in a tumor type is 5% rather than 20%, then there is 10.5% chance that there will be at least 3 responses in 23 subjects (false positive rate).

Endpoints:

Safety:

The primary objective is to characterize the safety and tolerability of monotherapy nivolumab. The primary objective will be measured by:

- Number and percent of subjects that experience drug-related grade 3-4 AEs occurring up to 100 days after the last dose of study drug. [Time Frame - On a continuous basis up to 100 days after the last dose of study drug];
- Number and percent of subjects that experience drug-related grade 3-4 SAEs occurring up to 100 days after the last dose of study drug. [Time Frame - On a continuous basis up to 100 days after the last dose of study drug];
- Number and percent of subjects with clinical laboratory abnormalities by worst toxicity grade by NCI CTCAE version 4.0 (as assessed at the planned times listed in section 5.1). [Time Frame - On a continuous basis up to 100 days after the last dose of study drug].

Pharmacokinetics: Cmax, Cmin, Tmax, T-HALF, AUC(0-T), AUC(TAU) pharmacokinetic parameters derived from serum concentration versus time data.

Efficacy: Individual best overall response (BOR), duration of response, objective response rate (ORR), progression free survival rate (PFSR), and overall survival.

[redacted]

Analyses:

Pharmacokinetic Analyses: Summary statistics will be tabulated for the pharmacokinetics parameters of nivolumab by dose and study week, as appropriate. To describe the dependency on dose, scatter plots of nivolumab Cmax and AUC(0-T) versus dose will be provided for each day measured. To assess attainment of steady state, plots of Cmin versus time will be provided.

Pharmacokinetic concentrations from limited samples after the first dose will be listed, and may be used in combination with other studies for exposure-response or population pharmacokinetic modeling, which will be part of a separate report.

Immunogenicity Analyses: A listing will be provided of all available immunogenicity data. Additionally, a listing of immunogenicity data from those subjects with at least one positive ADA at any time point will be provided by dose regimen. The frequency of subjects with at least one positive ADA assessment, and frequency of subjects who develop ADA after a negative baseline assessment will be provided by dose. The frequency of neutralizing antibodies will be provided based on data availability. To examine the potential relationship between immunogenicity and safety, the frequency and type of AEs of special interest may be examined by overall immunogenicity status. Associations between pre-dose concentrations of nivolumab and corresponding ADA assessments may be explored.

Safety Analyses: All recorded adverse events will be listed and tabulated by system organ class, preferred term, and dose and coded according to the most current version of MedDRA across disease types. A subset of adverse event tables may be summarized by disease type. The incidence of adverse events will be reviewed for potential significance and clinical importance. Vital signs and clinical laboratory test results will be listed and summarized by dose. Any significant physical examination findings and results of clinical laboratory tests will be listed. ECG results will be evaluated by the investigator and abnormalities, if present, will be listed.

Efficacy Analyses: Individual best overall response (BOR), duration of response and PFS will be listed, using appropriate response criteria for each disease type: the IMWG Uniform Response Criteria for Multiple Myeloma, standard criteria for Lymphoma, the Clinical End Points and Response Criteria in Mycosis Fungoides and Sezary Syndrome for cutaneous T cell Lymphoma, and cytogenic, hematologic and molecular response criteria for CML. BOR outcomes will be tabulated by disease type and dose. The objective response rate (ORR) and corresponding 95% exact confidence interval will be provided by tumor type. The median duration of response and PFSR at select time points and corresponding two-sided 95% confidence intervals will be estimated by Kaplan-Meier methodology, by disease type, depending on data availability. The analysis of overall survival would be exploratory. Kaplan-Meier plots of PFS and overall survival will be provided by tumor type. ORR, duration of response and PFS analyses will include subjects in the dose expansion phase and subjects in the dose escalation phase matching those in the dose expansion phase by disease type and dose. Individual changes in the tumor burden over time may be presented graphically based on data availability within a disease type.

Radiographic images may be collected for blinded independent central review. Details of this analysis will be documented in a separate document.

Biomarker Analyses: The potential association between PD-L1 expression levels as measured by immunohistochemistry and clinical efficacy measures will be assessed using methods such as Fisher's exact test if sample size is large enough to allow meaningful analysis or other methodology as appropriate.

The pharmacodynamic effect of nivolumab on exploratory biomarkers will be assessed by summary statistics and investigated graphically. Patterns of change in these exploratory biomarkers over time and how the patterns differ among dose levels may be investigated using appropriate modeling, for example, by linear mixed effects models.

IPILIMUMAB/NIVOLUMAB COHORTS

For the combination of nivolumab and ipilimumab administered concurrently, data will be compared to that obtained from subjects who were enrolled previously in the nivolumab monotherapy portion of this study.

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Intravenous (IV) infusion of nivolumab at doses of 1 mg/kg or 3 mg/kg and ipilimumab at doses of 1 mg/kg or 3 mg/kg. Therapy will be administered every three weeks for four doses followed by nivolumab alone at 3 mg/kg every 2 weeks for a total of two years of therapy.

Study Phase: 1

Research Hypothesis: The purpose of these combination cohorts is to evaluate the safety profile and tolerability, and to identify dose limiting toxicities (DLT) and a tolerated dose of the combination of nivolumab and ipilimumab in subjects with select relapsed or refractory hematologic malignancies.

Objective(s):

Primary Objective: To establish the dose limiting toxicities and a tolerated dose of the combination of nivolumab and ipilimumab in subjects with select relapsed or refractory hematologic malignancies.

Secondary Objectives:

- To characterize the pharmacokinetics of nivolumab and ipilimumab when administered in combination.
- To characterize the immunogenicity of nivolumab and ipilimumab when administered in combination.
- To assess the preliminary anti-tumor activity of nivolumab and ipilimumab when administered in combination.
- To assess the potential association between PD-L1 expression on tumor cells as measured by immunohistochemistry and clinical efficacy measures of nivolumab and ipilimumab when administered in combination.

[redacted]

Study Design: Subjects will receive study drug as detailed in Figure 2.

Figure 2: Study Design for IPILIMUMAB/NIVOLUMAB Cohorts

Study Population
Approx. 75

Tumor Cohort
Multiple Myeloma (approximately 14 pts)
Hodgkin/PMBL (approximately 32 pts)
B cell lymphoma (approximately 14 pts)
- diffuse large B cell lymphoma or follicular lymphoma
T cell lymphoma (approximately 14 pts)
3 mg/kg of nivolumab and
1 mg/kg of ipilimumab
four doses
followed by nivolumab alone at 3 mg/kg

Study Population: Subjects with the following relapsed or refractory tumors: Multiple Myeloma, Hodgkin Lymphoma, Primary Mediastinal B Cell Lymphoma, Diffuse Large B Cell Lymphoma, Follicular Lymphoma, and T cell Lymphoma are eligible. Subjects with the following are excluded: myelodysplasia, polycythemia vera, idiopathic thrombocythemia, myelofibrosis, acute and chronic leukemias, T cell lymphoblastic lymphoma or Burkitt lymphoma. Subjects with autoimmune disorders are excluded.

Study Assessments:

Safety Evaluation: Adverse events will be assessed continuously during the study and for 100 days post last treatment. Adverse events will be coded using the most current version of MedDRA and reviewed for potential significance and importance. Adverse events will be evaluated according to the NCI CTCAE Version 4.0. Subjects should be followed until all treatment related adverse events have recovered to baseline or are deemed irreversible by the investigator.

Pharmacokinetic Evaluation: Blood samples for pharmacokinetic assessments of nivolumab and ipilimumab will be collected from all subjects at specified time points.

Efficacy Evaluation: Subjects with non-Hodgkin's lymphoma or Hodgkin lymphoma will be evaluated using the International Workshop to Standardize Response Criteria for non-Hodgkin's Lymphomas (Appendix 1), subjects with cutaneous T cell lymphoma with the Clinical End Points and Response Criteria in Mycosis Fungoides and Sezary Syndrome (Appendix 2) and subjects with multiple myeloma with the International Myeloma Working Group Uniform Response Criteria to define response and progressive disease (Appendix 3). Radiographic images may be collected for blinded independent central review.

Immunogenicity Evaluation: Blood samples to evaluate development of positive anti-drug antibody (ADA) response will be collected to each of nivolumab and ipilimumab at specified time points for all subjects.

Biomarker Evaluation: The pharmacodynamic characteristics of nivolumab in combination with ipilimumab will be assessed by quantifying biomarkers in peripheral blood and tumor tissue (when collected). Biomarkers will also be analyzed in peripheral blood and tumor tissue in order to identify markers that may predict response to treatment. Residual sample material available after completion of the designated analyses may be used in the future for identification of additional pharmacodynamic or predictive markers or to enhance understanding of disease biology.

Statistical Considerations:

Sample Size: In a tumor cohort, if 3 (21%) or 4 (29%) responses are observed with 14 subjects in each cohort, then the lower limit of the 90% one-sided confidence intervals for the objective response rate would be 8% and 13% respectively. These calculations are based on the Clopper-Pearson method for exact confidence intervals.

In addition, if the true ORR in a tumor cohort is 20% then with 14 patients in each cohort there is 80% chance of observing at least 2 responses and 96% chance of observing at least 1 response, or 20% chance of observing 0 or 1 response (false negative rate) and 4% chance of observing 0 response (false negative rate). If the true ORR in a tumor cohort is 5% rather than 20%, then there is 15% chance that there will be at least 2 responses in 14 subjects (false positive rate).

Endpoints:

Safety:

The primary objective is to characterize the safety and tolerability of nivolumab and ipilimumab. The primary objective will be measured by:

- Number and percent of subjects that experience drug-related grade 3-4 AEs occurring up to 100 days after the last dose of study drug. [Time Frame - On a continuous basis up to 100 days after the last dose of study drug];
- Number and percent of subjects that experience drug-related grade 3-4 SAEs occurring up to 100 days after the last dose of study drug. [Time Frame - On a continuous basis up to 100 days after the last dose of study drug];
- Number and percent of subjects with clinical laboratory abnormalities by worst toxicity grade by NCI CTCAE version 4.0 (as assessed at the planned times listed in section 5.1). [Time Frame - On a continuous basis up to 100 days after the last dose of study drug].

Pharmacokinetics: PK parameters including Cmax, Cmin, Ceoinf, Tmax, AUC(0-T), and AUC(TAU) of nivolumab and ipilimumab derived from serum concentration versus time data.

Efficacy: Individual best overall response (BOR), duration of response, objective response rate (ORR), progression free survival rate (PFSR) and overall survival for all treated subjects, and mSWAT score for subjects with cutaneous T cell lymphoma.

Immunogenicity: The frequency of baseline ADA positive subjects and ADA positive subjects.

Biomarker: PD-L1 expression levels as measured by immunohistochemistry.

Analyses:

Pharmacokinetic Analyses: Summary statistics will be tabulated for the pharmacokinetic parameters of nivolumab and/or ipilimumab by treatment, disease type, dose and study week and a subset of subjects in the tumor cohorts following the full PK profile sampling schedule. Cmin will be summarized for all subjects. To describe the dependency on dose, scatter plots of nivolumab Cmax and AUC(0-T) versus dose will be provided for each day measured treatment and study drug. To assess attainment of steady state, plots of Cmin versus time will be provided by treatment and by study drug for all subjects. Pharmacokinetic concentrations of nivolumab and ipilimumab from all subjects will be listed, and may be used in combination with other studies for exposure response or population pharmacokinetic modeling, which will be part of a separate report.

Immunogenicity Analyses: A listing will be provided of all available immunogenicity data. Additionally, a listing of immunogenicity data from those ADA positive subjects will be provided. The frequency of baseline positive subjects, and frequency of ADA positive subjects will be provided by treatment and dose. The frequency of neutralizing antibodies will be provided based on data availability. To examine the potential relationship between immunogenicity and safety, the frequency and type of AEs of special interest may be examined by overall immunogenicity status. Associations between pre-dose concentrations of nivolumab and ipilimumab, biomarkers, efficacy and corresponding ADA assessments may be explored.

Safety Analyses: All recorded adverse events will be listed and tabulated by system organ class, preferred term, treatment, and dose and coded according to the most current version of MedDRA across disease types. A subset of adverse event tables may be summarized by disease type. The incidence of adverse events will be reviewed for potential significance and clinical importance. Vital signs and clinical laboratory test results will be listed and summarized by treatment and dose. Any significant physical examination findings and results of clinical laboratory tests will be listed. ECG results will be evaluated by the investigator and abnormalities, if present, will be listed.

Efficacy Analyses: Individual BOR, duration of response and PFS will be listed, using appropriate response criteria for each disease type: the IMWG Uniform Response Criteria for Multiple Myeloma, standard criteria for Lymphoma, the Clinical End Points and Response Criteria in Mycosis Fungoides and Sezary Syndrome for cutaneous T cell Lymphoma. BOR outcomes will be tabulated by disease type, treatment and dose. The ORR and corresponding 95% exact confidence interval will be provided by tumor type. The median duration of response and PFSR at select time points and corresponding two-sided 95% confidence intervals will be estimated by Kaplan-Meier methodology, by disease type, depending on data availability. The analysis of overall survival would be exploratory. Kaplan-Meier plots of PFS and overall survival will be provided by tumor type. ORR, duration of response and PFS analyses will include subjects in tumor cohorts and subjects in exploratory schedule evaluation matching those in tumor cohorts by disease type, treatment and dose. Individual changes in the tumor burden over time may be presented graphically based on the availability of data within a disease type. To evaluate the response in skin for subjects with cutaneous T cell lymphoma, the percentage change from baseline on the mSWAT score will be derived and listed.

Radiographic images may be collected for blinded independent central review. Details of this analysis will be documented in a separate document.

Biomarker Analyses: The potential association between PD-L1 expression levels as measured by immunohistochemistry and clinical efficacy measures will be assessed using methods such as Fisher's exact test if sample size is large enough to allow meaningful analysis or other methodology as appropriate. The pharmacodynamic effect of monotherapy nivolumab and combination therapy with nivolumab and ipilimumab on exploratory biomarkers will be assessed by summary statistics and investigated graphically. Patterns of change in these exploratory biomarkers over time and how the patterns differ among dose levels may be investigated using appropriate modeling, for example, by linear mixed effects models.

LIRILUMAB/NIVOLUMAB COHORTS

For the combination of nivolumab and lirilumab administered concurrently, data will be compared to that obtained from subjects who were enrolled previously in the nivolumab monotherapy portion of this study.

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Intravenous (IV) infusion of nivolumab 3 mg/kg and lirilumab 3 mg/kg. Nivolumab will be administered every 2 weeks and lirilumab will be administered every 4 weeks (in combination with nivolumab) for up to two years of study therapy total.

Study Phase: 1

Research Hypothesis: The purpose of these combination cohorts is to evaluate the safety profile and tolerability of the combination of nivolumab and lirilumab in subjects with select relapsed or refractory hematologic malignancies.

Objective(s):

Primary Objective: To establish the tolerated dose of the combination of nivolumab and lirilumab in subjects with select relapsed/refractory hematologic malignancies.

Secondary Objectives:

- To characterize the pharmacokinetics of nivolumab and lirilumab when administered in combination
- To characterize the immunogenicity of nivolumab and lirilumab when administered in combination
- To assess the preliminary anti-tumor activity of nivolumab and lirilumab when administered in combination
- To assess the potential association between PD-L1 expression on tumor cells as measured by immunohistochemistry and clinical efficacy measures of nivolumab and lirilumab when administered in combination

[redacted]

Study Design: Subjects will receive study drug as detailed in Figure 3.

Figure 3: **Study Design for Nivolumab and Lirilumab Combination Therapy**

Study Population

Approx. 130

Tumor Cohort

Multiple Myeloma (approximately 20 pts)

Hodgkin/PMBL (approximately 20 pts)

B cell lymphoma (approximately 60 pts)

- diffuse large B cell lymphoma or follicular lymphoma only (approximately 30 each)

T cell lymphoma (approximately 30 pts)

3 mg/kg of nivolumab given every 2 weeks

3 mg/kg of lirilumab given every 4 weeks

Study Population: Subjects with the following relapsed or refractory tumors: Hodgkin Lymphoma/Primary Mediastinal B Cell Lymphoma, T cell Lymphoma, B Cell Lymphoma (Diffuse Large B Cell Lymphoma and Follicular Lymphoma only), and Multiple Myeloma. Subjects with the following are excluded: myelodysplasia, polycythemia vera, idiopathic thrombocythemia, myelofibrosis, acute and chronic leukemias, T cell lymphoblastic lymphoma or Burkitt lymphoma. Subjects with autoimmune disorders are excluded.

Study Assessments:

Safety Evaluation: Adverse events will be assessed continuously during the study and for 100 days post last treatment. Adverse events will be coded using the most current version of MedDRA and reviewed for potential significance and importance. Adverse events will be evaluated according to the NCI CTCAE Version 4.0. Subjects should be followed until all treatment related adverse events have recovered to baseline or are deemed irreversible by the investigator.

Pharmacokinetic Evaluation: Blood samples for pharmacokinetic assessments of nivolumab and lirilumab will be collected from all subjects at specified time points.

Efficacy Evaluation: Subjects with non-Hodgkin's lymphoma or Hodgkin lymphoma will be evaluated using the International Workshop to Standardize Response Criteria for non-Hodgkin's Lymphomas (Appendix 1), subjects with cutaneous T cell lymphoma with the Clinical End Points and Response Criteria in Mycosis Fungoides and Sezary Syndrome (Appendix 2) and subjects with multiple myeloma with the International Myeloma Working Group Uniform Response Criteria to define response and progressive disease (Appendix 3). Radiographic images may be collected for blinded independent central review.

Immunogenicity Evaluation: Blood samples to evaluate development of positive anti-drug antibody (ADA) response will be collected to each of nivolumab and lirilumab at specified time points for all subjects.

Biomarker Evaluation: The pharmacodynamic characteristics of nivolumab in combination with lirilumab will be assessed by quantifying biomarkers in peripheral blood and tumor tissue (when collected). Biomarkers will also be analyzed in peripheral blood and tumor tissue in order to identify markers that may predict response to treatment.

Residual sample material available after completion of the designated analyses may be used in the future for identification of additional pharmacodynamic or predictive markers or to enhance understanding of disease biology.

Statistical Considerations:

Sample Size: In a tumor cohort, if 4 (20%) or 5 (25%) responses are observed with 20 subjects in each cohort, then the lower limit of the 90% one-sided confidence intervals for the objective response rate would be 9% and 13% respectively. In a tumor cohort, if 3 (10%) or 6 (20%) responses are observed with 30 subjects in each cohort, then the lower limit of the 90% one-sided confidence intervals for the objective response rate would be 4% and 11% respectively. These calculations are based on the Clopper-Pearson method for exact confidence intervals.

In addition, if the true ORR in a tumor cohorts is 20% then with 20 patients in each cohort there is 93% chance of observing at least 2 responses, or 7% chance of observing 0 or 1 response (false negative rate). If the true ORR in a tumor type is 5% rather than 20%, then there is 26% chance that there will be at least 2 responses in 20 subjects (false positive rate). If the true ORR in a tumor cohort is 20% then with 30 patients in each cohort there is 88% chance of observing at least 4 responses, or 12% chance of observing 3 or fewer responses (false negative rate). If the true ORR in a tumor type is 5% rather than 20%, then there is 6% chance that there will be at least 4 responses in 30 subjects (false positive rate).

Approximately 130 subjects are expected to be enrolled in tumor cohorts.

Endpoints:

Safety:

The primary objective is to characterize the safety and tolerability of nivolumab and lirilumab. The primary objective will be measured by:

- Number and percent of subjects that experience drug-related grade 3-4 AEs occurring up to 100 days after the last dose of study drug. [Time Frame - On a continuous basis up to 100 days after the last dose of study drug];
- Number and percent of subjects that experience drug-related grade 3-4 SAEs occurring up to 100 days after the last dose of study drug. [Time Frame - On a continuous basis up to 100 days after the last dose of study drug];
- Number and percent of subjects with clinical laboratory abnormalities by worst toxicity grade by NCI CTCAE version 4.0 (as assessed at the planned times listed in section 5.1). [Time Frame - On a continuous basis up to 100 days after the last dose of study drug].

Pharmacokinetics: PK parameters including Cmax, Cmin, Ceoinf, Tmax, AUC(0-T), and AUC(TAU) of nivolumab and lirilumab derived from serum concentration versus time data.

Efficacy: Individual best overall response (BOR), duration of response, objective response rate (ORR), progression free survival rate (PFSR) and overall survival for all treated subjects, and mSWAT score for subjects with cutaneous T cell lymphoma.

Immunogenicity: The frequency of baseline ADA positive subjects and ADA positive subjects.

Biomarker: PD-L1 expression levels as measured by immunohistochemistry.

Analyses:

Pharmacokinetic Analyses: Summary statistics will be tabulated for the pharmacokinetic parameters of nivolumab in the presence of lirilumab by treatment, disease type, dose and study week. Cmin will be summarized for all subjects. To describe the dependency on dose, scatter plots of nivolumab Cmax and AUC(0-T) versus dose will be provided for each day measured treatment and study drug. To assess attainment of steady state, plots of Cmin versus time will be provided by treatment and by study drug for all subjects. Pharmacokinetic concentrations of nivolumab and lirilumab from all subjects will be listed, and may be used in combination with other studies for exposure response or population pharmacokinetic modeling, which will be part of a separate report.

Immunogenicity Analyses: A listing will be provided of all available immunogenicity data. Additionally, a listing of immunogenicity data from those ADA positive subjects will be provided. The frequency of baseline positive subjects, and frequency of ADA positive subjects will be provided by treatment and dose. The frequency of

neutralizing antibodies will be provided based on data availability. To examine the potential relationship between immunogenicity and safety, the frequency and type of AEs of special interest may be examined by overall immunogenicity status. Associations between pre-dose concentrations of nivolumab and lirilumab, biomarkers, efficacy and corresponding ADA assessments may be explored.

Safety Analyses: All recorded adverse events will be listed and tabulated by system organ class, preferred term, treatment, and dose and coded according to the most current version of MedDRA across disease types. A subset of adverse event tables may be summarized by disease type. The incidence of adverse events will be reviewed for potential significance and clinical importance. Vital signs and clinical laboratory test results will be listed and summarized by treatment and dose. Any significant physical examination findings and results of clinical laboratory tests will be listed. ECG results will be evaluated by the investigator and abnormalities, if present, will be listed.

Efficacy Analyses: Individual BOR, duration of response and PFS will be listed, using appropriate response criteria for each disease type: the IMWG Uniform Response Criteria for Multiple Myeloma, standard criteria for Lymphoma, the Clinical End Points and Response Criteria in Mycosis Fungoides and Sezary Syndrome for cutaneous T cell Lymphoma. BOR outcomes will be tabulated by disease type, treatment and dose. The ORR and corresponding 95% exact confidence interval will be provided by tumor type. The median duration of response and PFSR at select time points and corresponding two-sided 95% confidence intervals will be estimated by Kaplan-Meier methodology, by disease type, depending on data availability. The analysis of overall survival would be exploratory. Kaplan-Meier plots of PFS and overall survival will be provided by tumor type. ORR, duration of response and PFS analyses will include subjects in tumor cohorts by disease type, treatment and dose. Individual changes in the tumor burden over time may be presented graphically based on the availability of data within a disease type. To evaluate the response in skin for subjects with cutaneous T cell lymphoma, the percentage change from baseline on the mSWAT score will be derived and listed.

Radiographic images may be collected for blinded independent central review. Details of this analysis will be documented in a separate document.

Biomarker Analyses: The potential association between PD-L1 expression levels as measured by immunohistochemistry and clinical efficacy measures will be assessed using methods such as Fisher's exact test if sample size is large enough to allow meaningful analysis or other methodology as appropriate. The pharmacodynamic effect of combination therapy with lirilumab on exploratory biomarkers will be assessed by summary statistics and investigated graphically. Patterns of change in these exploratory biomarkers over time and how the patterns differ among dose levels may be investigated using appropriate modeling, for example, by linear mixed effects models.

TABLE OF CONTENTS

[redacted]

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

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

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

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

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

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

2.2 Institutional Review Board/Independent Ethics Committee

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

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

2.3 Informed Consent

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

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

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

Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4) Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
5) If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed HIPAA Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is a Phase 1, open-label, multicenter, dose-escalation, and multidose study of nivolumab a fully human monoclonal IgG4 antibody targeting the PD-1 membrane receptor on T cells.

The study will consist of Screening (up to 28 days), Treatment (up to 2 years), and Follow-up (up to 12 months) with the possibility of Retreatment and Follow up (up to 12 months and 100 days) (See Figure 3.1-1). The first dose administered will be followed by a three week period for pharmacokinetic and pharmacodynamic assessment of nivolumab. A response assessment following administration of the first dose will be obtained. Therapy will be given on an every two week schedule thereafter with response assessment performed at Weeks 8, 16, 24, and then every 16 weeks thereafter. The scheduled response assessments must be completed before the next dose of therapy.

IPILIMUMAB/NIVOLUMAB COHORTS

Combination cohorts will evaluate the combination of nivolumab and ipilimumab.

The study will consist of Screening (up to 28 days), Treatment (up to 2 years), and Follow-up. See Figure 3.1-2.

LIRILUMAB/NIVOLUMAB COHORTS

Combination cohorts will evaluate the combination of nivolumab and lirilumab.

The study will consist of Screening (up to 28 days), Treatment (up to 2 years), and Follow-up. See Figure 3.1-3.

Figure 3.1-1: Study Design for Nivolumab Monotherapy

Subjects will receive study drug as detailed in Figure 3.1-1. The operating characteristics of 6+3 design in the dose escalation phase is examined in Appendix 5.

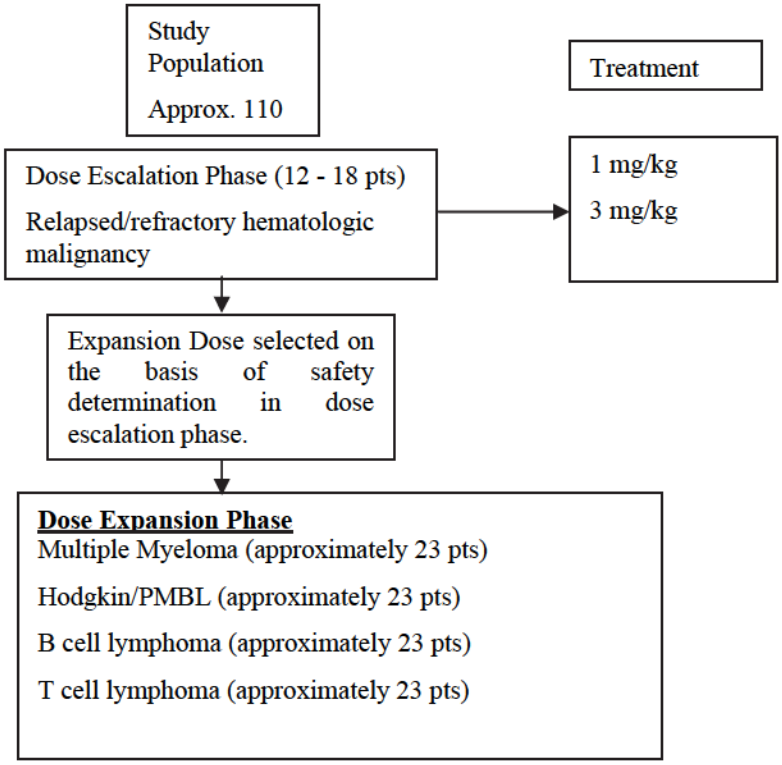


Figure 3.1-2: Study Design for Nivolumab and Ipilimumab Combination Therapy

Subjects will receive study drug as detailed in Figure 3.1-2.

Study Population

Approx. 75

Tumor Cohort

Multiple Myeloma (approximately 14 pts)

Hodgkin/PMBL (approximately 32 pts)

B cell lymphoma (approximately 14 pts)

- diffuse large B cell lymphoma or follicular lymphoma

T cell lymphoma (approximately 14 pts)

3 mg/kg of nivolumab and

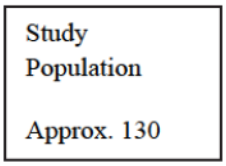
1 mg/kg of ipilimumab

four doses

followed by nivolumab alone at 3 mg/kg

Figure 3.1-3: Study Design for Nivolumab and Lirilumab Combination Therapy

Subjects will receive study drug as detailed in Figure 3.1-3.



Tumor Cohort

Multiple Myeloma	(approximately 20 pts)
Hodgkin/PMBL	(approximately 20 pts)
B cell lymphoma	(approximately 60 pts)
- diffuse large B cell lymphoma or follicular lymphoma only	(approximately 30 each)
T cell lymphoma	(approximately 30 pts)

3 mg/kg of nivolumab given every 2 weeks

3 mg/kg of lirilumab given every 4 weeks

3.1.1 Dose Evaluation

A 6 + 3 design with escalating dose cohorts will be used with this Phase 1 study starting at 1 mg/kg and escalating to 3 mg/kg. Subjects will be assigned to a dose level in the order of study entry.

The first cohort will receive nivolumab at the 1 mg/kg dose level. Enrollment into the next cohort cannot begin until 2 weeks after the administration of the third dose (after 7 weeks) of nivolumab to the last patient in the previous cohort. Up to 6 subjects will be treated at each dose level with expansion to 9 subjects if two dose-limiting toxicities are observed in the first 6 subjects. If dose limiting toxicity occurs at the first dose level, the study of lower doses of nivolumab may be investigated. If less than 2 DLTs occur in a cohort of 6 subjects, a new cohort of 6 subjects will be treated at the next higher dose level. If 2 of 6 subjects in a cohort experience a DLT, that cohort will be expanded to 9 subjects. If only 1 of the 6 subjects experiences a DLT, then the next cohort of 6 subjects will be treated at the next higher dose level. If 3 or more DLTs occur within a cohort, then that dose level will be above the maximum tolerated dose (MTD; the highest dose tested where no more than 1 of 6 or 2 of 9 subjects has experienced a DLT), and new subjects will be enrolled at the previous lower (tolerated) dose level. Frequent

monitoring of hematologic parameters with dose interruption or discontinuation parameters is included in the study. If a dose of 1 mg/kg is above the MTD, a lower dose may be considered by protocol amendment.

IPILIMUMAB/NIVOLUMAB COHORTS

Subjects in tumor cohorts will be treated at a dose of 3 mg/kg nivolumab in combination with 1 mg/kg ipilimumab. The combination will be administered every 3 weeks for 4 doses, followed by monotherapy with nivolumab at 3 mg/kg every 2 weeks for up to 2 years of study therapy total. All adverse event data will be monitored on an ongoing basis for safety. If the above dose is not acceptable, then alternative doses may be considered, including 1 mg/kg nivolumab in combination with 3 mg/kg ipilimumab or 1 mg/kg nivolumab in combination with 1 mg/kg ipilimumab.

LIRILUMAB/NIVOLUMAB COHORTS

See Section 3.1.2 Expansion Cohorts

3.1.1.1 Dose Limiting Toxicity

Dose limiting toxicity (DLT) will be determined based on the incidence and intensity of drug related adverse events (AEs) occurring up to two weeks after the administration of the third dose of nivolumab or 7 weeks after initiation of therapy whichever is longer.

IPILIMUMAB/NIVOLUMAB COHORTS

Dose limiting toxicity (DLT) will be determined based on the incidence and intensity of drug related adverse events (AEs) occurring within 3 cycles (9 weeks) of combination therapy. Subjects who experience delays will remain evaluable for safety, if they receive 3 cycles within 12 weeks. Toxicity will be graded by CTCAE v 4.0.

Dose Limiting Hepatic Toxicity

DLT will be hepatotoxicity as evidenced by any of the following:

- AST or ALT > 5 - 10X ULN for > 2 weeks
- AST or ALT > 10X ULN irrespective of duration
- AST or ALT > 8X ULN irrespective of duration (only for IPILIMUMAB/NIVOLUMAB COHORTS
- Total bilirubin > 5X ULN irrespective of duration
- Concurrent AST or ALT > 3X ULN and total bilirubin > 2X ULN (potential Hy's Law case)

Dose Limiting Hematologic Toxicity

- Grade 4 neutropenia lasting more than 5 days
- Febrile neutropenia of any duration (ANC < 1.0 x 10^9/L, fever > 38.5 degrees Celsius)
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding or any requirement for platelet transfusion

- Grade 4 anemia, unexplained by underlying disease

Dose Limiting Non-hematologic Toxicity

Grade 2 or greater eye pain or reduction of visual acuity that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks of starting therapy or requires systemic treatment.

Clinically relevant Grade 3 or greater non-hepatic and non-hematologic toxicity excluding lymphopenia, asymptomatic lipase or amylase or laboratory abnormalities that correct to grade 1 within 72 hours after treatment. Toxicity will be graded by CTCAE v 4.0.

DLTs that occur after the decision to dose escalate will be used to determine the recommended phase 2 dose for this population.

No dose escalations or de-escalations are permitted within each subject's treatment. A subject who is withdrawn from the study before the completion of the first seven weeks of treatment (before 3 cycles and 9 weeks for subjects enrolled in the IPILIMUMAB/NIVOLUMAB COHORTS) or a reason other than a DLT may be replaced. Subjects who experience dose limiting toxicity may resume treatment as per Section 4.1.7 upon resolution, providing that criteria for permanent discontinuation are not met (Section 4.1.9).

The occurrence of clinically meaningful drug related AEs requires early recognition and prompt intervention. Management algorithms are available for suspected pulmonary, gastrointestinal, hepatic, renal, endocrine, neurological and skin toxicities. The recommendation is to follow the nivolumab IB adverse event algorithm.

3.1.2 Expansion Cohorts

To further characterize safety and efficacy 4 expansion cohorts will be enrolled. These hematologic malignancies were selected based on the expression of PD-L1 by the tumor or expression of PD-1 on infiltrating T cells in the tumor. The diseases that will be explored are HL/PMBL, T cell lymphoma, B cell lymphoma and multiple myeloma. A total of 6 or 9 subjects must be enrolled at the MTD (or the highest dose studied where ≤ 1 of 6 or ≤ 2 of 9 subjects experiences a DLT if the MTD is not identified) before any subject is dosed in the expansion cohorts. If none of the first 5 subjects have a DLT by the end of seven weeks of treatment in the dose escalation phase of the study, enrollment to the primary expansion cohorts can begin immediately following the enrollment of the sixth subject. Archived tumor tissue from every surgical resection should be obtained and submitted for biomarker analysis

IPILIMUMAB/NIVOLUMAB COHORTS

To further characterize safety and efficacy, 4 tumor cohorts will be enrolled. All subjects in the 4 tumor cohorts will be required to have archived tumor tissue available at the time of screening, and will be required to undergo tumor biopsy while on-study (see Table 5.1-6). Archived tumor tissue from every surgical resection should be obtained and submitted for biomarker analysis. If archived tumor is not available at the time of screening, the subject must agree to undergo

biopsy before the administration of study therapy and also while on-study (see Table 5.1-6). At the time of the biopsy while on-study, the PI will determine if there have been significant changes in the clinical course to suggest that subjects can no longer undergo biopsy safely. These subjects will continue therapy, but may be replaced. The diseases that will be explored are HL/PMBL, T cell lymphoma, B cell lymphoma (diffuse large B cell lymphoma and follicular lymphoma only), and multiple myeloma.

LIRILUMAB/NIVOLUMAB COHORTS

Subjects in tumor cohorts will be treated at a dose of 3 mg/kg nivolumab in combination with 3 mg/kg lirilumab. Nivolumab will be administered every 2 weeks and lirilumab will be administered every 4 weeks (in combination with nivolumab) for up to two years of study therapy total. All adverse event data will be monitored on an ongoing basis for safety. If the above dose is not acceptable, then alternative doses may be utilized, including 3 mg/kg nivolumab in combination with 1 mg/kg lirilumab.

To characterize safety and efficacy, four tumor cohorts will be enrolled. The diseases that will be explored are HL/PMBL, T cell lymphoma, B cell lymphoma (diffuse large B cell lymphoma and follicular lymphoma only), and multiple myeloma. All subjects in the four tumor cohorts will be required to have archived tumor tissue available at the time of screening. Archived tumor tissue from every surgical resection should be obtained and submitted for biomarker analysis. If archived tumor is not available at the time of screening, the subject must agree to undergo biopsy before the administration of study therapy. Subjects will also be required to undergo tumor biopsy while on-study Table 5.1-9. At the time of the biopsy while on-study, the PI will determine if there have been significant changes in the clinical course to suggest that subjects can no longer undergo biopsy safely. These subjects may continue therapy.

Guidelines for Continuation of Therapy

Response assessment will be evaluated using the appropriate response criteria in Appendices 1, 2, and 3. Response assessments for all subjects will occur at the specified intervals (results of assessments must be reviewed and documented before the next dose of treatment, with the exception of subjects with multiple myeloma, if the result will not change the decision to administer the dose).

The expected duration of treatment on this study is 2 years. If a subject is eligible to continue receiving treatment, the next dose should be given no earlier than 14 (±) 2 days, or 21 (±) 2 days when nivolumab and ipilimumab are given together, and no later than 6 weeks after the last dose of the prior treatment to maximize dose intensity. No subject will be permitted dose escalations or de-escalations.

Subjects who meet the following conditions will continue to be treated:

- Subjects with a best overall response (BOR) of complete response (CR), partial response (PR) or stable disease (SD) will continue to receive study drug until the first occurrence of either: 1) achievement of a confirmed CR; 2) clinical deterioration suggesting that no further benefit from treatment is likely; 3) meets criteria for discontinuation of study therapy as

outlined in Sections 3.1.1.1 Dose Limiting Toxicity and 3.5 Discontinuation of Subjects from Treatment; 4) other intolerability to therapy; or 5) administration of 2 years of therapy

- Unconfirmed CR: Subject will receive an additional cycle of treatment until confirmation of the CR at the next scheduled imaging time point
- Confirmed CR: Subjects will stop treatment and enter the first Follow-Up Period
- PR or stable disease (SD): Subjects will continue to receive study drug until confirmed CR, PD (under the conditions defined below), toxicity (as defined below), or for 2 years. Subjects will then enter the first Follow-up Period
- PD: Accumulating evidence indicates that the emergence of objective responses to agents that activate anti-tumor immune responses follows delayed kinetics of weeks or months, and can be preceded by initial apparent radiological progression or the appearance of new lesions or some enlarging lesions while certain target lesions are regressing ("mixed response"). It is thus reasonable, in the absence of clinical deterioration, to continue to treat these subjects until progression is both confirmed and found to have worsened at a subsequent imaging evaluation. Evidence of PD will be based on a comparison with baseline (or nadir) scans or other evaluations.

Subjects with PD should be managed in the study as follows:

Subjects will be permitted to continue study therapy beyond PD as measured by the appropriate evaluation criteria as long as they meet the following criteria:

- Clinical benefit as assessed by the investigator
- Disease progression is not rapid
- Tolerance of study drug
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
- Subjects have provided written informed consent prior to receiving additional treatment with nivolumab and ipilimumab.

The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment. The decision to continue treatment should be discussed with the BMS Medical Monitor and documented in the study records. Palliative radiotherapy or surgical resection of isolated lesions is permitted in these subjects and will not preclude the continued treatment with study therapy.

Subjects should discontinue study therapy upon evidence of further progression, defined as an additional 10% or greater increase in tumor burden volume from the time of initial progression (including all target lesions and new measurable lesions) or similar criteria in tumor types without measurable lesions.

Subjects who experience AEs that require discontinuation while receiving both nivolumab and ipilimumab may be allowed to continue therapy with nivolumab only, if deemed in their best interest by both the PI and the BMS medical monitor. Subjects must be deriving clinical benefit.

Subjects who experience AEs that require discontinuation while receiving both nivolumab and lirilumab may be allowed to continue therapy with nivolumab only, if deemed in their best interest by both the PI and the BMS medical monitor. Subjects must be deriving clinical benefit.

Re-initiation of Study Therapy for Subjects in Follow-up Period

Subjects entering the follow-up period with ongoing disease control (ongoing CR, PR, or SD) may reinitiate study therapy upon confirmed disease progression after discussion and agreement with the BMS Medical Monitor. Subjects reinitiating study therapy should continue to meet eligibility criteria at the time study drug resumes and should not have experienced a DLT requiring permanent discontinuation of study therapy. Subjects will receive study therapy at the same dose level that they received prior to entering the follow-up period. Subjects that resume study therapy in this setting may receive study therapy for up to one additional year. Subjects who have completed 1 year of follow-up without evidence of disease progression will not be considered eligible for re-initiation of study therapy. Additional safety and efficacy summaries will be presented for those subjects who reinitiated study therapy.

IPILIMUMAB/NIVOLUMAB COHORTS

Subjects enrolled in the nivolumab and ipilimumab combination cohorts will not be eligible for re-initiation of study therapy for progression in the follow-up period.

LIRILUMAB/NIVOLUMAB COHORTS

Subjects enrolled in the nivolumab and lirilumab combination cohorts will not be eligible for re-initiation of study therapy for progression in the follow-up period.

3.1.3 Stopping Rules

3.1.3.1 Stopping Rules for Clinical Deterioration

Accumulating evidence indicates that the emergence of objective responses to agents that activate anti-tumor immune responses follows delayed kinetics of weeks or months, and can be preceded by initial apparent radiological progression or appearance of new lesions or some enlarging lesions while certain target lesions are regressing ("mixed response"). It is thus reasonable to allow for these possibilities and continue to treat the subject until progression is confirmed and found to be advancing and continuing at the next imaging assessment. These considerations should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment.

Such deterioration will be assessed to have occurred after a clinical event that, in the Investigator's opinion, is attributable to disease progression, is unlikely to reverse with continued study treatment and therefore indicates that the subject is not benefiting from study treatment and cannot be managed by the addition of supportive care (such as bisphosphonates and/or bone

directed radiotherapy, thoracentesis or paracentesis of accumulating effusions). The decision to continue or stop treatment should be discussed with the BMS Medical Monitor and will be documented in the study files.

Examples of events that may, in the Investigator's opinion, indicate a lack of clinical benefit include, but are not limited to, the following:

- Performance status decrease of at least 2 points from baseline
- skeletal related events defined by the following:
  - pathologic bone fracture in the region of cancer involvement
  - cancer related surgery to bone
  - spinal cord or nerve root compression
- Bladder outlet or uretheral obstruction
- Development of new central nervous system metastases
- Any setting where the initiation of new anti-neoplastic therapy has been deemed beneficial to the subject even in the absence of any such documented clinical events.

3.2 Post Study Access to Therapy

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

3.3 Study Population

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

3.3.1 Inclusion Criteria

1. **Signed Written Informed Consent**
   - **a)** Voluntary signed and dated IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not a part of standard of care
2. **Target Population**
   - **a)** ECOG Performance of 0 or 1. (See Appendix 4)
   - **b)** Subjects must have histological confirmation of relapsed or refractory hematologic malignancy
   - **c)** Subjects with non-Hodgkin lymphoma or Hodgkin lymphoma must have at least one measureable lesion > 1.5 cm as defined by lymphoma response criteria. Subjects must

also have an additional lesion that is amenable for biopsy. Subjects with cutaneous T cell lymphoma do not require a measureable lesion. Subjects with lesions in a previously radiated field as the sole site of measurable disease will be permitted to enroll provided the lesion has demonstrated clear progression and can be measured accurately. (See Appendix 1)

d) Subjects with cutaneous T cell lymphoma must have measurable disease by mSWAT (See Appendix 2)

e) Subjects with MM must have detectable disease as measured by presence of monoclonal immunoglobulin protein in a serum electrophoresis: IgG, IgA, IgM, (M-protein ≥ 0.5 g/dl or serum IgD M-protein ≥ 0.05 g/dl) or serum free-light chain or 24 hour urine with free light chain. Excluded are subjects with only plasmacytomas, plasma cell leukemia, or non-secretory myeloma

f) Subjects must be more than 100 days post autologous transplant

g) Life expectancy of at least 3 months

h) For subjects with lymphoma, must have a fresh biopsy or either an archived formalin fixed tissue block, or 7 to 15 slides of tumor sample for performance of correlative studies. All subjects in the nivolumab/ipilimumab and nivolumab/lirilumab cohorts must have a fresh biopsy or either an archived formalin fixed tissue block, or 7 to 15 slides of tumor sample for performance of correlative studies. Archived tumor tissue from every surgical resection should be obtained and submitted for biomarker analysis.

i) Subjects must have received at least one prior chemotherapy regimen. Subjects must be off therapy for at least 3 weeks (3 weeks for subcutaneous, 2 weeks for oral agents, 1 week for topical agents) prior to Day 1

j) Prior palliative radiation must have been completed at least 2 weeks prior to study Day 1

k) Toxicities related to prior therapy must have returned to Grade 1 or less, except for alopecia. Peripheral neuropathy must be Grade 2 or less

l) Adequate bone marrow function defined as:

- **i)** Absolute neutrophil count ≥ 1000/µl (stable off any growth factor within 1 week of study drug administration) (2)Hemoglobin ≥ 9g/dL (transfusion to achieve this level is permitted) (3)Platelet count ≥ 50 X 10^3/µl (transfusion to achieve this level is not permitted)

m) Adequate renal parameters defined as:

- **i)** CrCl > 40 ml/min (Cockcroft-Gault formula)
- **ii)** Adequate hepatic parameters defined as:
  - **(1)** AST ≤ 3 x ULN
  - **(2)** ALT ≤ 3 x ULN
  - **(3)** Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert's Syndrome, who must have a total bilirubin < 3.0 mg/dL and direct bilirubin < 0.5 mg/dL

n) Ability to comply with treatment, PK, and immune-monitoring sample collection (when indicated) and required study follow up

o) Oxygen saturation ≥ 94% at rest, without oxygen supplementation

p) Approval to undergo on-treatment biopsy

q) Subjects with Hodgkin lymphoma or non Hodgkin's lymphoma can have a history of brentuximab vedotin treatment or be brentuximab vedotin naive to be eligible. Subjects are not required to have failed brentuximab vedotin treatment to be eligible for the study

r) Subjects with CD 30 positive anaplastic large cell lymphoma must have a history of prior treatment with brentuximab vedotin

s) Subjects with follicular lymphoma must have received ≥ 2 prior treatment lines; each of the two prior treatment lines must include rituximab and/or an alkylating agent

t) Subjects with Diffuse Large B Cell Lymphoma (DLBCL) must have relapsed after high dose conditioning chemotherapy and ASCT or after failure of at least one prior multi-agent chemotherapy regimen in subjects who are ineligible for ASCT.

u) Subjects with Multiple Myeloma must have failed at least 2 prior regimens to include receiving an immunomodulatory agent and a proteasome inhibitor

v) Subjects with a prior history of chemotherapy-induced or radiation-induced pulmonary toxicity require confirmation of diffusing capacity of the lung for carbon monoxide (DLCO) over 60% (adjusted for hemoglobin) by a pulmonary function test prior to study enrollment

w) Normal thyroid hormone levels/function at baseline including subjects who are controlled with hormone replacement therapy

3. Age and Reproductive Status

a) (See Section 3.3.3 for the definition of WOCBP) Men and women ≥ 18 years of age

b) Women of childbearing potential (WOCBP) must use highly effective methods of birth control for up to 23 weeks after the last dose of investigational product to minimize the risk of pregnancy. WOCBP must follow instructions for birth control for the entire duration of the study including a minimum of 23 weeks after dosing has been completed.(See Appendix 6 for birth control instructions)

c) Women must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of investigational product

d) Women must not be breastfeeding

e) Sexually active fertile men must use highly effective birth control if their partners are WOCBP. Men that are sexually active with WOCBP must follow instructions for birth control for the entire duration of the study and a minimum of 31 weeks after dosing has been completed.

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Subjects with myelodysplasia, polycythemia vera, idiopathic thrombocythemia, myelofibrosis, acute leukemias, CML, T cell lymphoblastic or Burkitt lymphoma

b) Subjects with a history of central nervous system involvement by hematologic malignancy or symptoms suggestive of central nervous system involvement

c) Subjects with a history of chest radiation ≤ 24 weeks prior to first dose of study medication

d) Subjects who were exposed to ≥ 1000 mg of BCNU as part of a conditioning regimen

2. Medical History and Concurrent Diseases

a) Subjects with concomitant second malignancies (except adequately treated non-melanomatous skin cancers, melanoma in situ surgically resected, carcinoma in situ of the breast, superficial bladder cancer, prostate cancer or in situ cervical cancers) are excluded unless a complete remission was achieved as it is empirically determined based on the malignancy and treatment provided prior to study entry and no additional therapy is required or anticipated to be required during the study period

b) Subjects with any active autoimmune disease or a history of known or suspected autoimmune disease, or history of syndrome that requires systemic corticosteroids or immunosuppressive medications, except for subjects with vitiligo, resolved childhood asthma/atopy, controlled thyroid disorders

c) A serious uncontrolled medical disorder or active infection which would impair the ability of the subject to receive protocol therapy or whose control may be jeopardized by the complications of this therapy

d) Deep vein thrombosis not adequately controlled

e) Uncontrolled or significant cardiovascular disease including, but not limited to any of the following:

i) myocardial infarction or stroke/TIA within the past 6 months

ii) uncontrolled angina within the past 3 months

iii) any history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation or torsades de pointes)

iv) QTc prolongation > 480 msec

v) history of other clinically significant heart disease (ie, cardiomyopathy, congestive heart failure with NYHA functional classification III-IV, pericarditis, significant pericardial effusion)

vi) requirement for daily supplemental oxygen therapy

f) Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137 or anti CTLA-4 antibody (or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways). Prior therapy with an anti-KIR antibody

g) Not applicable per Protocol Amendment 07

h) Non-oncology vaccine therapies for prevention of infectious diseases (eg HPV vaccine) within 4 weeks of study drug administration. The inactivated seasonal influenza vaccine can be given to subjects before treatment and while on therapy without restriction. Influenza vaccines containing live virus or other clinically indicated vaccinations for infectious diseases (ie, pneumovax, varicella, etc.) may be permitted; but must be discussed with the Sponsor's Medical Monitor and may require a study drug washout period prior to and after administration of vaccine (not applicable after amendment 011)

i) Prior organ allograft or allogeneic bone marrow transplantation

j) Subjects with symptomatic interstitial pneumonitis

3. **Physical and Laboratory Test Findings**
   - **a)** Positive for human immunodeficiency virus (HIV 1/2) antibody (may obtain additional testing or substitute testing per institutional guidelines to rule out infection), or known acquired immunodeficiency syndrome (AIDS)
   - **b)** Positive tests for hepatitis B virus surface antigen (HBsAg) or hepatitis C antibody (may obtain additional testing or substitute testing per institutional guidelines to rule out infections).
   - **c)** Ejection fraction less than 50%
4. **Allergies and Adverse Drug Reaction**
   - **a)** History of Grade 4 anaphylactic reaction to monoclonal antibody therapy
5. **Sex and Reproductive Status**
   - **a)** WOCBP who are unwilling or unable to use an acceptable method to minimize the risk of pregnancy for the entire study period and for at least 23 weeks after the last dose of investigational product.
   - **b)** Women who are pregnant or breastfeeding
   - **c)** Women with a positive pregnancy test on enrollment or prior to investigational product administration
   - **d)** Sexually active fertile men not using effective birth control if their partners are WOCBP for at least 31 weeks after the last dose of investigational product.
6. **Other Exclusion Criteria**
   - **a)** Prisoners or subjects who are involuntarily incarcerated
   - **b)** Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria. No exception to the entry criteria is permitted.

3.3.3 Women of Childbearing Potential

Women of childbearing potential (WOCBP) include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy), and who is not postmenopausal. Post menopause is defined as:

- Amenorrhea ≥ 12 consecutive months without another cause, and a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL or
- Women with irregular menstrual periods and a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL or
- NOTE: FSH level testing is not required for women ≥ 62 years old with amenorrhea of ≥ 1 year
- Women on hormone replacement therapy (HRT)

Women who are using oral or other hormonal contraceptives, such as vaginal products, skin patches, or implanted or injectable products, or mechanical products, such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides), to prevent pregnancy or who are practicing abstinence or who have a sterile (eg, vasectomy) partner should be considered to be of childbearing potential.

3.4 Concomitant Treatments

Subjects are permitted the use of topical, ocular, intranasal, intra-articular, and inhalational corticosteroids (with minimal systemic absorption). Immunosuppressive doses (eg, prednisone > 10 mg/day or equivalent) and/or physiologic replacement doses of systemic corticosteroids (eg, prednisone 10 mg/day) are permitted in the context of treating adverse events. A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

3.4.1 Prohibited and/or Restricted Treatments

- Concurrent chemotherapy, hormonal therapy or immunotherapy regimens
- Systemic corticosteroids (doses greater than prednisone 10 mg/day or equivalent) within 7 days of study entry are prohibited.
- Concurrent immunosuppressive agents
- Concurrent use of Rank Ligand inhibitors
- Vaccines except as noted in Section 3.4.
- Bisphosphonates are allowed for the treatment of bone pain or hypercalcemia.

3.4.2 Other Restrictions and Precautions

3.4.2.1 Treatment of Infusion Reactions

Infusion reactions should be graded according to CTCAE Version 4.0 allergic reaction/hypersensitivity. These reactions may manifest with signs and symptoms that may include, but are not limited to fever, chills, headache, rash, pruritus, arthralgias, hypo-or hypertension, bronchospasm or other symptoms. Severe infusion reactions require the immediate interruption of study drug therapy and permanent discontinuation from further treatment. Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Subjects should be carefully observed until the complete resolution of all signs and symptoms. Following an infusion reaction, subjects should be premedicated with acetaminophen and diphenhydramine for future treatments.

Nivolumab, ipilimumab and lirilumab contain only human immunoglobulin protein sequences. However, infusion reactions have been observed. If such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritis, arthralgias, hypo- or hypertension,

bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as a SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE (version 4.0) guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated)

The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional study drug administrations.

For Grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, iv fluids]; prophylactic medications indicated for ≤ 24 hours)

Stop the study drug infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve. Monitor subject closely. If symptoms recur then no further study drug will be administered at that visit. Subsequent infusions should be administered over 2 hours. The amount of study drug infused must be recorded on the case report form (CRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional study drug administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of SoluCortef or equivalent) may be used.

For Grade 3 or Grade 4 symptoms: (Severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]. Grade 4: life-threatening; pressor or ventilatory support indicated). Immediately discontinue infusion of study drug. Begin an IV infusion of normal saline, and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Study drug will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized

pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

3.5 Discontinuation of Subjects from Treatment

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

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event (AE), abnormal laboratory test results or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Grade 3or 4 uveitis
- Unable to reduce corticosteroids to 10 mg or less of prednisone or equivalent per day within 12 weeks
- Pregnancy
- Termination of the study by BMS
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Documented and confirmed disease progression or clinical deterioration while receiving active study therapy
- Stopping rules as defined in Section 3.1.3.

All subjects who discontinue should comply with protocol specified follow-up procedures as outlined in Section 5. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If a subject was withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate case report form (CRF) page.

4 TREATMENTS

Study drugs include both Noninvestigational (NIMP) and Investigational Medicinal Products (IMP) and can consist of the following:

- All products, active or placebo, being tested or used as a comparator in a clinical trial
- Study required premedication, and
- Other drugs administered as part of the study that are critical to claims of efficacy (eg, backbone therapy, rescue medications)

4.1 Study Treatments

For product descriptions see Table 4.1-1. Non-investigational medicinal product will be used to treat infusion reactions as described in Section 3.4.2.1.

Table 4.1-1: Product Description - Treatment Period

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
BMS-936558-01 (nivolumab) Solution for injection	100 mg (10 mg/mL)	10 mL vial/ Open-Label	5 or 10 vials per carton/ Open-Label	Clear to opalescent, colorless to pale yellow liquid. May contain particles.	2 - 8°C Protect from light and freezing.
Ipilimumab Solution for Injection	200 mg (5 mg/mL)	40 mL per vial/Open-label	4 vials per carton/Open-label	Clear, colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect from light and freezing.
BMS-986015-01 (lirilumab) Solution for injection	100 mg (10 mg/mL)	10 ml vial/open-label	6 vials per carton/ Open-label	Clear to opalescent, colorless liquid. Essentially free of particles	2 to 8°C Protect from light and freezing.

4.1.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, investigational product(s) is/are: nivolumab, ipilimumab and lirilumab.

4.1.2 Noninvestigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as noninvestigational products.

In this protocol, noninvestigational products is/are: medications listed in Section 3.4.2.1 used to treat infusion reactions. These are sourced by the investigator as are all drug administration supplies.

4.1.3 Handling and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the sponsor. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact the sponsor immediately.

Investigational product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

For nivolumab, ipilimumab, and lirilumab, please refer to the current IB/pharmacy reference sheets for storage, handling and preparation instructions.

4.1.3.1 Study Drug Preparation and Administration

BMS-936558 (nivolumab) is to be administered as a 60 minute IV infusion. Ipilimumab is to be administered as a 90 minute infusion. Lirilumab is to be administered as a 60 minute IV infusion.

When both study drugs are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the

ipilimumab or lirilumab infusion. The second infusion will always be ipilimumab or lirilumab, and will start no sooner than 30 minutes after completion of the nivolumab infusion.

4.1.4 Dose Modifications

There will be no dose adjustments allowed for study drugs with the exception of changes due to fluctuations in weight.

4.1.5 Intrasubject Dose Escalation

No intrasubject dose escalation will be allowed.

4.1.6 Dose Reductions

Study drug dose reductions are not permitted in this study.

4.1.7 Criteria to Resume Treatment

IPILIMUMAB/NIVOLUMAB COHORTS and LIRILUMAB/NIVOLUMAB COHORTS

DOSE DELAY CRITERIA

Dose delay criteria apply for all drug-related adverse events attributed to nivolumab, ipilimumab, or both.

- Any DLT criteria
- Any persistent Grade 2 AE (with the exception of fatigue, weakness, skin AEs, laboratory abnormalities). Treatment may resume when the AE resolves to Grade 1.
- AST or ALT > 3X ULN. Treatment may resume when the AE resolves to Grade 1.
- Any adverse event, laboratory abnormality, or condition that, in the judgment of the investigator, warrants delaying the dose of study medication.

If dose delay is necessary, both nivolumab and ipilimumab must be delayed until treatment can resume. If a delay prevents subsequent infusion of ipilimumab, the dose of ipilimumab should be replaced as soon as possible. At least 19 days must elapse between the replacement dose of ipilimumab and the administration of the next dose of the combination.

If dose delay is necessary, both nivolumab and lirilumab must be delayed until treatment can resume. If a delay prevents subsequent infusion of lirilumab, the dose of lirilumab should be replaced as soon as possible.

Subjects may resume treatment when the drug-related AE(s) resolve(s) to Grade 1 or baseline value (except for grade 2 fatigue, grade 2 weakness, asymptomatic lipase or amylase) for which subjects are not required to delay treatment) unless the AE meets the criteria for permanent discontinuation (Section 4.1.9) Comprehensive algorithms for supportive care for subjects treated with nivolumab are included in this protocol (see Appendix 7). Subjects must resume treatment within 6 weeks from the previous dose. Treatment may be resumed after 6 weeks if the PI and BMS medical monitor agree that the benefit/risk justify continuing study therapy.

In the case of endocrine-related AEs, hormone replacement therapy may be utilized to restore physiologic function and to permit retreatment with study drug. If this is not possible the subject must be discontinued from study therapy.

4.1.8 Infusion Delays and Missed Doses

In the case that an infusion cannot be administered at a scheduled visit, it has to be administered as soon as possible. If the delay is between 1 and 7 days, the procedures at the original scheduled visit should be performed. If the delay is more than 7 days, the procedures at the next visit should be performed. Response assessment should never be skipped. Subjects with infusion delays of greater than 6 weeks should normally discontinue treatment and enter the Follow-up Period with the exception of delays related to prophylactic vaccinations as outlined in Section 3.4.1 or after specific consultation and agreement between the investigator and BMS Medical Monitor in settings where benefit/risk may justify continued study therapy (eg, subject deriving clinical benefit who requires prolonged steroid taper for management of non-DLT AEs).

4.1.9 Permanent Discontinuation Due to Adverse Event(s)

Subjects will be required to permanently discontinue study therapy for the following drug related adverse events:

1) Any DLT as defined in Section 3.1.1.1, with the following exceptions:
   a) grade 3 fever that returns to grade 1 or less within 3 days, and is not associated with hemodynamic compromise (including hypotension, or clinical or laboratory evidence of end organ perfusion impairment)
   b) grade 3 diarrhea, nausea, vomiting, or abdominal pain that returns to grade 1 or baseline within 3 days with medical intervention
   c) grade 3 pruritus or rash that returns to grade 1 or baseline within 7 days or baseline with medical intervention
   d) grade 3 endocrinopathy that is well controlled by hormone replacement
   e) grade 3 tumor flare (defined as pain, irritation or rash that localizes to sites of known or suspected tumor)
2) Subjects who develop recurrent grade 3 treatment related adverse reactions should be permanently discontinued from study drug.

The consideration to re-initiate study therapy under these exceptions will be made on a case by case basis after considering the overall benefit/risk profile and in consultation between the investigator and the study sponsor. In cases where the adverse event meets the criteria for permanent discontinuation from study therapy, but the investigator and the sponsor believe that re-initiation of study therapy may be potentially beneficial and justified, details will be submitted in advance to the FDA for review, prior to re-initiation of study therapy.

4.1.10 Discontinuation Due to Confirmed Complete Response

Subjects with a CR may continue to receive study therapy until response confirmation or for an additional 16 weeks (whichever is longer) and then enter the follow-up period. Subjects that achieve a confirmed complete response and enter follow-up may be eligible for additional study therapy upon confirmed disease progression as described in protocol in Section 3.1.2. Subjects enrolled in the nivolumab and ipilimumab or nivolumab and lirilumab combination cohorts will not be eligible for additional study therapy if they progress during the follow-up period.

4.2 Method of Assigning Subject Identification

After informed consent has been obtained, the subject must be enrolled into the study by calling an interactive voice response system (IVRS) to obtain the subject number. The exact procedure for using the IVRS will be detailed in a separate document.

4.3 Selection and Timing of Dose for Each Subject

Subjects will be entered sequentially into the dose level currently accruing up to a maximum of 6. If a DLT occurs in two subjects, that level will be expanded to include 9 subjects. Once the determination that the dose level is safe has been made, the next level can begin accrual.

4.4 Blinding/Unblinding

Not applicable.

4.5 Treatment Compliance

Study drug will be administered in the clinical facility. The investigator or their designated study personnel will maintain a log (Drug Accountability Log) of all study drugs received dispensed and destroyed. The investigator and the study personnel will ensure that each subject receives the calculated dose of the study drug based on body weight.

Drug supplies will be inventoried and accounted for throughout the study. The Drug Accountability Log will be reviewed by the study monitor during site visits and at the completion of the study. Any discrepancy should be brought to the attention of the Sponsor.

4.6 Destruction and Return of Study Drug

4.6.1 Destruction of Study Drug

For this study, study drugs (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials and syringes may be destroyed on site.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible BMS Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.

- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met the responsible BMS Study Monitor will make arrangements for return of study drug.

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

4.6.2 Return of Study Drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible BMS Study Monitor.

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

[redacted]

5.2 Study Materials

- Instructions and kits for collections, processing and shipment of blood and tissue samples
- Investigator Brochure
- Local laboratory data entry instructions
- IVRS registration instructions
- Study drug supplies
- CRF Instructions
- SAE forms
- Pregnancy Surveillance Forms
- CTCAE version 4.0.

5.3 Safety Assessments

Adverse events will be assessed continuously during the study and for 100 days post last treatment. Adverse events will be coded using the most current version of MedDRA and reviewed for potential significance and clinical importance. Adverse events will be evaluated according to the NCI CTCAE Version 4.0 dated June 14, 2010. Subjects should be followed until all treatment-related adverse events have recovered to baseline or are deemed irreversible by the investigator.

5.4 Efficacy Assessments

Efficacy assessment will be conducted and reported on the eCRF using the appropriate efficacy assessment based on tumor type. Subjects with non-Hodgkin's lymphoma or Hodgkin lymphoma will be evaluated using the International Workshop to Standardize Response Criteria for non-Hodgkin's Lymphomas (Appendix 1), subjects with multiple myeloma with the International Myeloma Working Group Uniform Response Criteria to define response and progressive disease (Appendix 3), and subjects with cutaneous T cell Lymphoma with the Clinical End Points and Response Criteria in Mycosis Fungoides and Sezary Syndrome[76] (Appendix 2). Radiographic images may be collected for blinded independent central review.

5.4.1 Tumor biopsy and Bone Marrow Biopsy and Aspiration

Tumor biopsies will be collected to evaluate the immune infiltrate and tumor for expression of immune modulating proteins, such as PD-L1 and LAG-3, prior to and during study therapy. Prior to therapy, archived tumor tissue from every surgical resection should be obtained and submitted for biomarker analysis. During the tumor cohorts phase of the study, core tumor biopsies will be mandated for all subjects in all four tumor cohorts. All other subjects may volunteer to undergo biopsies at any time during therapy if deemed clinically safe. Core tumor biopsies may be obtained from clinically palpable tumors or visualized by imaging studies. The investigator, in consultation with the radiology staff, must determine the degree of risk associated with the procedure and find it acceptable. Excisional biopsies may also be performed to obtain tumor

biopsy samples. Invasive procedures that require general anesthesia should not be performed to obtain a biopsy specimen. If a surgical procedure is performed for a clinical indication, then that sample may be used for research purposes if the subject consents to its use. Bone marrow biopsies and aspirates will be obtained using institutional standards for these procedures. Fine needle aspirates are not allowed because the architecture of the tumor in its microenvironment cannot be assessed.

When subjects are considered for re-initiation of therapy in the follow-up period, investigators are strongly encouraged to collect an additional core biopsy prior to re-initiation of therapy, if determined to be of acceptable clinical risk. Biopsy of tumor in this setting will aid in identifying potential mechanisms of escape from anti-tumor effects of nivolumab. This biopsy will also be prepared for FFPE and fresh frozen sections.

Lymphoma Cohorts:

During the tumor cohorts phase of the study, four core tumor biopsies will be required for all subjects in the Hodgkin lymphoma, B cell lymphoma and T cell lymphoma cohorts. These biopsies should be obtained prior to therapy and prior to week 7 (prior to week 9 for subjects in the nivolumab/lirilumab cohorts). The pre-treatment biopsy is not required if archived sample that is from a recent biopsy (within four months of initiation of study drug) is available (either a formalin fixed block or 7-15 slides that contain tumor). This will be utilized for IHC analyses. If a fresh tumor biopsy is collected, two cores will be placed in formalin for IHC analysis and the remaining will be placed in RNAlater solution to be utilized for RNA analysis as described in Section 5.6. On-treatment biopsies for all patients with lymphoma will otherwise be optional. Collection of 4 cores is ideal. Nevertheless, if this is not possible due to safety concerns or other medical reasons, collection of fewer core biopsies is acceptable. Priority should be placed on placing cores in formalin for IHC analysis. If 3 cores are taken, place 2 cores in formalin and 1 in RNAlater. If 2 cores are taken, place 1 in formalin and 1 in RNAlater. If 1 core is taken, place 1 core in formalin. See Table 5.1-6 and Table 5.1-9 for collection time points.

Multiple Myeloma Cohorts:

During the tumor cohorts phase of the study, two bone marrow biopsies and aspirates will be required for all subjects in the myeloma cohort. The first biopsy should be obtained prior to therapy. All patients on this study are required to undergo bone marrow biopsy and aspiration at the time of screening to rule out myelodysplasia. Therefore, at this time, one additional core sample and 16 ml of aspirate should be obtained. The second biopsy should be obtained prior to week 7 (prior to week 9 for subjects in the nivolumab/lirilumab cohorts). These samples will be utilized for exploratory analysis of immune function and receptor occupancy that is described in Section 5.6. On-treatment bone marrow biopsy and aspiration for all patients with bone marrow involvement will otherwise be optional. Bone marrow biopsy and aspiration may also be required as part of standard clinical care, such as to document progression and to document complete response. Extra biopsy and aspirate samples should be obtained if possible to allow for research assessment as listed above. See Table 5.1-6 and Table 5.1-9 for collection time points.

5.5 Pharmacokinetic Assessments

5.5.1 Pharmacokinetic Collection & Processing

Table 5.1-4 lists the sampling schedule to be followed for all subjects in the nivolumab monotherapy cohorts. Table 5.1-7 lists the sampling schedule to be followed in the combination cohorts; 5 subjects in each of the tumor cohorts will follow the full PK profile schedule, the remaining subjects in the tumor cohorts will follow the sparse sampling schedule. Table 5.1-9 lists the sampling schedule to be followed in the lirilumab combination cohorts. Cmin will be reported for all subjects with available data for the assessment of pharmacokinetics. Serial samples will be collected after the first dose and at additional time points. All on-treatment predose and end-of-infusion PK time-points are intended to align with days on which study drug is administered. If dosing occurs on a different day, the PK sampling should be adjusted accordingly. Further details of sample collection, processing and shipment are provided in the laboratory manual.

5.5.2 Pharmacokinetic Sample Analyses

The serum samples will be analyzed for nivolumab and/or ipilimumab and/or lirilumab by validated methods. In addition, selected serum samples may be analyzed by an exploratory analytical method that measures nivolumab and/or ipilimumab and/or lirilumab for technology exploration purposes; exploratory results will not be reported.

[redacted]

[redacted]

[redacted]

[redacted]

5.9 Results of Central Assessments

Not applicable.

6 ADVERSE EVENTS

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

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

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

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

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

6.1 Serious Adverse Events

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

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity

- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI).

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

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

NOTE:

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

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

6.1.1 Serious Adverse Event Collection and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 100 days of discontinuation of dosing.

The investigator should report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). When using paper forms, the reports are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: See Contact Information list.

SAE Facsimile Number: See Contact Information list.

For studies capturing SAEs/pregnancies through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

SAE Telephone Contact (required for SAE and pregnancy reporting): See Contact Information list.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

A ***nonserious adverse event*** is an AE not classified as serious.

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects. All non-serious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study drug treatment.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

6.4 Pregnancy

If, following initiation of the investigational product, it is discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours and in accordance with SAE reporting procedures described in Section 6.1.1.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information, must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 Overdose

An overdose is defined as accidental or intentional administration of any dose of product that is considered both excessive and medically important. All occurrences of overdose must be reported as SAEs (see Section 6.1.1 for reporting details).

6.6 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1 for reporting details).

Potential drug induced liver injury is defined as

1) AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

3) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

Not applicable.

8 STATISTICAL CONSIDERATIONS

[redacted]

[redacted]

[redacted]

[redacted]

8.2 Populations for Analyses

- All Enrolled Subjects: All subjects who sign informed consent form and were registered in IVRS.
- All Treated Subjects: All subjects who receive at least one dose of nivolumab and/or ipilimumab and/or lirilumab.
- Response Evaluable Subjects: All treated subjects with measurable disease at baseline and one of the following: 1) at least one on-treatment efficacy assessment, 2) clinical progression, or 3) death.
- Pharmacokinetic (PK) Subjects: All subjects who receive at least one dose of study medication and have available serum concentration data.
- Biomarker Subjects: All subjects who receive at least one dose of study medication and have available biomarker data
- Immunogenicity Subjects: All subjects who receive at least one dose of study medication and have available ADA data.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

8.3.1.1 Safety

The primary objective relates to establishing the dose limiting toxicities and maximum tolerated dose for monotherapy with nivolumab, combination therapy with nivolumab and ipilimumab, and combination therapy with nivolumab and lirilumab in subjects with select relapsed/refractory hematologic malignancies. This objective will be measured by the following endpoints:

- Number and percent of subjects that experience drug-related grade 3-4 AEs occurring up to 100 days after the last dose of study drug. [Time Frame - On a continuous basis up to 100 days after the last dose of study drug];

- Number and percent of subjects that experience drug-related grade 3-4 SAEs occurring up to 100 days after the last dose of study drug. [Time Frame - On a continuous basis up to 100 days after the last dose of study drug];
- Number and percent of subjects with clinical laboratory abnormalities by worst toxicity grade by NCI CTCAE version 4.0 (as assessed at the planned times listed in Section 5.1). [Time Frame - On a continuous basis up to 100 days after the last dose of study drug].

8.3.2 Secondary Endpoint(s)

8.3.2.1 Efficacy

The secondary objective relating to efficacy is to assess the preliminary antitumor activity of various doses of monotherapy nivolumab, the combination of nivolumab and ipilimumab, and the combination of nivolumab and lirilumab in subjects with relapsed/refractory hematologic malignancy. This objective will be measured by tabulations of individual BOR and analyses of the ORR, duration of response, and PFS. The BOR outcomes will be based on the disease specific criteria (specified in Appendices 1, 2, and 3).

Best Overall Response (BOR)

BOR is defined as the best response designation over the study as a whole, recorded between the date of first dose and the last efficacy assessment prior to subsequent therapy.

Progression Free Survival Rate (PFSR)

The PFSR is defined as the proportion of subjects remaining progression free or surviving to time t, where t = 8, 16 and 24 weeks for patients receiving monotherapy nivolumab, t = 7, 13, 21, and 29 weeks for patients receiving the combination of nivolumab and ipilimumab, and t = 9, 17, 25, and 41 weeks for patients receiving the combination of nivolumab and lirilumab. This probability will be calculated by the product limit method (Kaplan-Meier estimate) which takes into account censored data.

Progression free survival (PFS), computed for all treated subjects, is defined as the time between date of first dose of study therapy and date of progression or death, whichever occurs first. Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last efficacy assessment. Subjects who did not have any on study efficacy assessments will be censored on the date of the first dose of study drug.

Objective Response Rate (ORR)

Objective response rate is defined as the proportion of subjects whose BOR one of the following responses divided by the number of treated subjects (or response-evaluable subjects).

- For lymphoma and myeloma subjects whose BOR is either partial response (PR) or complete response (CR)

Duration of Objective Response

The duration of response is defined as the time when the measurement criteria are first met for objective response until the date of documented disease progression or death. For subjects who neither progress nor die, the duration of response will be censored at the date of their last disease assessment.

Modified Severity Weighted Assessment Tool (mSWAT)

Response in Skin for subjects with cutaneous T cell lymphoma is evaluated by the mSWAT score which is reported by investigators.[76]

8.3.2.2 Pharmacokinetic

The following pharmacokinetic parameters of nivolumab, ipilimumab, and lirilumab will be derived from serum concentration time profiles for all subjects receiving nivolumab monotherapy and subjects following the full PK profile sampling schedule in the combination cohorts (approximately five subjects in each of the tumor cohorts). Cmin will be reported for all subjects with available data. These parameters are used to measure the secondary objective related to pharmacokinetics.

Cmax - Maximum observed serum concentration

Tmax - Time of maximum observed serum concentration

In addition, the following parameters will be determined for all subjects:

Cmin - Serum concentration achieved at the end of dosing interval (trough concentration, all subjects)

AUC(0-T) -Area under the plasma concentration-time curve from time zero to the last time of the last quantifiable concentration.

AUC(TAU) - Area under the concentration-time curve in one dosing interval

Ceoinf - Serum concentration achieved at the end of study drug infusion

8.3.2.3 Immunogenicity

The secondary objective relating to immunogenicity will be measured by the ADA status both at the sample level and at the subject level. At the sample level a sample is characterized as baseline ADA-positive, ADA-positive or ADA-negative to each study drug. At the subject level, relevant ADA endpoints include proportion of subjects with a Baseline ADA-positive sample, and proportion of ADA-positive subjects for each study drug. Time points for collection are specified in Table 5.1-4, Table 5.1-7 and Table 5.1-9. Additional details will be presented in the SAP.

8.3.2.4 Biomarker

The secondary objective of associating PD-L1 expression levels with clinical efficacy measures will be assessed using PD-L1 expression levels by immunohistochemistry as specified in Table 5.1-4, Table 5.1-6, and Table 5.1-9 and secondary efficacy endpoints.

[redacted]

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Subject demographics and baseline characteristics including age, sex, race, ethnicity, weight, baseline disease diagnosis, and medical conditions will be summarized by treatment and dose level using descriptive statistics.

8.4.2 Efficacy Analyses

Individual best overall response (BOR), duration of response and PFS will be listed, using appropriate response criteria for each disease type: the IMWG Uniform Response Criteria for Multiple Myeloma, standard criteria for Lymphoma, and the Clinical End Points and Response Criteria in Mycosis Fungoides and Sezary Syndrome for cutaneous T cell Lymphoma.[76,82,83]

BOR outcomes will be tabulated by disease type, treatment and dose. The objective response rate (ORR) and corresponding 95% exact confidence interval will be provided by disease type. The median duration of response and PFSR at select time points (8, 16, and 24 weeks for patients receiving monotherapy nivolumab, 7, 13, 21, and 29 weeks for patients receiving the combination of nivolumab and ipilimumab and 9, 17, 25, and 41 weeks for patients receiving the combination of nivolumab and lirilumab) and corresponding two-sided 95% confidence intervals will be estimated by Kaplan-Meier methodology, by disease type, depending on data availability. The analysis of overall survival would be exploratory. Kaplan-Meier plots of PFS and OS will be provided. ORR, duration of response and PFS analyses will include subjects in the dose expansion phase and subjects in the dose escalation phase matching those in the dose expansion phase by disease type, treatment, and dose. Individual changes in the tumor burden over time may be presented graphically based on data availability within a tumor type.

To evaluate the response in skin for subjects with cutaneous T cell lymphoma, the percentage change from baseline on the mSWAT score will be derived and listed.

8.4.3 Safety Analyses

All recorded adverse events will be listed and tabulated by system organ class, preferred term, and dose and coded according to the most current version of MedDRA

All recorded adverse events will be listed and tabulated by system organ class, preferred term, treatment, dose and coded according to the most current version of MedDRA across disease types. A subset of adverse event tables may be summarized by disease type. DLTs will be described by treatment and dose. The incidence of adverse events will be reviewed for potential significance and clinical importance. AEs will be coded according to the most current version of MedDRA. Vital signs and clinical laboratory test results will be listed and summarized by treatment and dose. Any significant physical examination findings and results of clinical laboratory tests will be listed. ECG results will be evaluated by the investigator and abnormalities, if present, will be listed.

8.4.4 Pharmacokinetic Analyses

Summary statistics will be tabulated for the pharmacokinetic parameters of nivolumab, nivolumab in the presence of ipilimumab, and nivolumab in the presence of lirilumab by treatment, disease type, dose and study week as appropriate for all subjects receiving nivolumab monotherapy and subjects following the full PK profile sampling schedule in the combination cohorts (approximately five subjects in each of the tumor cohorts and subjects in the exploratory dose evaluation cohorts). Cmin will be summarized for all subjects. To describe the dependency on dose, scatter plots of Cmax and AUC(0-T) versus dose will be provided for each day measured by treatment and study drug. To assess attainment of steady state, plots of Cmin versus time will be provided by treatment and by study drug for all subjects. Pharmacokinetic concentrations of nivolumab, ipilimumab and lirilumab from all subjects will be listed, and may be used in combination with other studies for exposure-response or population pharmacokinetic modeling, which will be part of a separate report.

[redacted]

8.5 Interim Analyses

Administrative interim analyses may be performed at several times prior to completion of the study in order to facilitate program decisions and to support presentations or publications.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- BMS
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

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

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.

9.1.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to BMS.

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of investigational product (those supplied by BMS) is maintained at each study site where study drug and are inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- nonstudy disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to BMS
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

BMS will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained.

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paper or electronic SAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

Clinical Study Report and Publications A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected considering the following criteria:

- External Principal Investigator designated at protocol development
- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study require approval by BMS prior to publication or presentation and must adhere to BMS's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to BMS at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. BMS shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

9.3 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected considering the following criteria: Subject recruitment (eg, among the top quartile of enrollers)

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study require approval by BMS prior to publication or presentation and must adhere to BMS's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to BMS at the earliest practicable time for review, but

at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. BMS shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

10 GLOSSARY OF TERMS

Term	Definition
Adverse Reaction	An adverse event that is considered by either the investigator or BMS as related to the investigational product
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator Brochure for an unapproved investigational product)

11 LIST OF ABBREVIATIONS

ADA	Anti-drug antibody
ALT	Alanine aminotransferase
APC	Antigen presenting cells
AST	Aspartate aminotransferace
BOR	Best overall response
BORR	Best overall response rate
BP	Blood pressure
CI	Confidence interval
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good clinical practices
GCSF	Granulocyte colony stimulating factor
HBV SAg	Hepatitis B-virus surface antigen
HCV RNA	Hepatitis C virus ribonucleic acid
HIPAA	Health Information Portability and Accountability Act
HL	Hodgkin lymphoma
HLA	Human leukocyte antigen
HSCT	Hematopoietic stem cell transplant
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IP	Investigational product
IRB	Institutional Review Board
ITIM	Immunoreceptor tyrosine inhibitory motif
ITSM	Immunoreceptor tyrosine-based switch motif
IV	Intravenous
KIR	Killer immunoglobulin-like receptor
LFTs	Liver function tests
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major histocompatibility complex
MRI	Magnetic resonance imaging

MTD	Maximum-tolerated dose
NK	Natural killer
ORR	Objective response rate
PD	Progressive disease
PD-1	Programmed death-1
PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2
PET	Positron emission tomography
PMBL	Primary mediastinal B cell Lymphoma
PR	Partial response
SAE	Serious adverse event
SD	Stable disease
SNP	Single nucleotide polymorphism
TCR	T-cell receptor
ULN	Upper limit of normal
WBC	White blood cell
WOCBP	Women of child bearing potential