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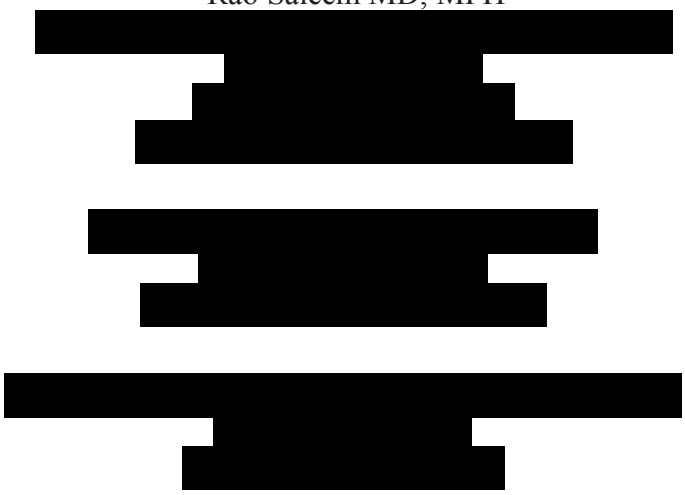
Clinical Protocol CA204142

A Phase 2, Multiple Cohort Study of Elotuzumab in Combination with Pomalidomide and Low-Dose Dexamethasone (EPd), and in Combination with Nivolumab (EN), in Patients with Multiple Myeloma Relapsed or Refractory to Prior Treatment with Lenalidomide.

Revised Protocol Number: 03

Study Director & Medical Monitor
Rao Saleem MD, MPH



to partners to which BMS has transferred obligations, eg, a Contract Research Organization (CRO).

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 03	08-Mar-2018	Major changes • Revisions required by the FDA based on safety concerns reported for patients treated in the Keynote 183 and Keynote 185 studies have been incorporated. • Incorporation of multiple myeloma program changes for biomarker evaluations of the elotuzumab in combination with nivolumab cohort (EN)
Revised Protocol 02	15-Feb-2017	Incorporate Amendment 02
Amendment 02	15-Feb-2017	• Allows subjects who received elotuzumab in combination with pomalidomide and low-dose dexamethasone (EPd Cohort) to receive nivolumab upon progression • Adds a cohort to receive elotuzumab in combination with nivolumab in a separate cohort (EN Cohort).
Revised Protocol 01	16-May-2016	Incorporates Amendment 01, Administrative Letters 01 and 02.
Amendment 01	16-May-2016	Major Changes • Patients with multiple myeloma who may have received prior treatment with elotuzumab outside of a clinical trial are now eligible, provided the patient did not discontinue treatment due to intolerability to elotuzumab • The requirement of 6 months or less for relapse to prior treatment with lenalidomide has been removed as a criteria for eligibility. • Monthly dosing of elotuzumab will now begin at Cycle 3 rather than at Cycle 7.
Administrative Letter 02	14-Dec-2015	Personnel changes
Administrative Letter 01	21-Sep-2015	Alignment of the following protocol sections with revised washout period for study drug: • Sections 3.3.1 Age and Reproductive Status • Table 5.1-3 Pregnancy Test Note • Table 5.3.4-1 Pregnancy Test Note • Section 6.4 Pregnancy
Original Protocol	27-Apr-2015	Not applicable

OVERALL RATIONALE FOR REVISED PROTOCOL 03:

[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Change in Medical Monitor	Administrative Change
[redacted]	[redacted]	[redacted]
• Synopsis Study Design • Section 3.1 Study Design and Duration • Figure 3.1-1 Study Design Schematic	Removed the option to add nivolumab to EPd cohort, removed the option to add pomalidomide/lenalidomide to the EN cohort, and added the option for EN patients to crossover to EPd if they not respond to EN treatment. Increased the EN cohort size to 30 patients.	[redacted]
• Synopsis Study Population • Section 3.3.1 Inclusion Criteria	Modified the number of prior lines and type of therapy a EN patient must have received to be eligible for enrollment	[redacted]
• Synopsis, Study Design • Section 3.3.4 Eligibility Criteria for EN Patients to Cross-over to EPd cohort	Added separate section to clarify eligibility criteria for crossover patients	[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
• Synopsis Statistical Considerations • Section 8 Statistical Considerations	Statistical sections have been updated to reflect changes in study design.	[redacted]
Section 1.1.6.2 Non-overlapping toxicities and preliminary safety	Added details about non-overlapping toxicities and preliminary safety data	[redacted]
[redacted]	[redacted]	[redacted]
Section 3.5 Discontinuation of Subjects following any Treatment with Study Drug	Modified to incorporate stopping rules and to reflect change in study design	[redacted]
Section 4.5 Selection and Timing of Dose For Each Subject	Tables updated to reflect changes in study design	[redacted]
Section 4.5.10 Stopping rules for unacceptable toxicity (EN cohort).	Added stopping rules for toxicity in the EN cohort	[redacted]
• Table 5.1-1 Screening; Screening Procedural Outline • Table 5.1-4 CA204142 Cycles 1 and 2 EN Cohort	Specifications for Bone Marrow Aspirates/Biopsy have been removed from the notes sections of the Time and Events tables along with specific assessment rows and replaced with a reference link to the sections and tables within the protocol that	[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
• Table 5.1-5 CA204142 Cycles 3 and 4 EN Cohort • Table 5.1-6 CA204142 Cycles 5 and beyond EN Cohort • Section 5.6.2.1 Bone Marrow Aspirate Samples	specify the bone marrow procedures and assessments.	
• Table 5.1-1 Screening; Screening Procedural Outline • [redacted]	Addition of Buccal Swab (Germ Line Control) for patients enrolled in EN cohort per Revised Protocol 03 and thereafter.	[redacted]
Table 5.1-4 CA204142 Cycles 1 and 2 EN Cohort	Deletion of specification for timing of thyroid function tests in notes	[redacted]
Section 5.4.2 Laboratory Assessments for Myeloma	Adjusted to reflect changes in study design	[redacted]
• Table 5.4.2-2, Bone Marrow Samples for EN Cohort • Section 5.6.2.1 Bone Marrow Aspirate Samples • Section 5.6.2.2 Peripheral Blood Samples Table 5.6.2.1-1 Usage of bone marrow aspirate samples (EN cohort).	Additional specifications for Bone Marrow Samples for EN Cohorts added.	[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]	[redacted]	[redacted]
Section 6.2.1 Nonserious Adverse Event Collection and Reporting	Specified that nonserious adverse events will be collected until 100 days from the last dose of study drug for EN and crossover subjects only. NSAEs will still be collected for 60 days in EPd cohort.	[redacted]
Section 9.2.2 Study Records	Dexamethasone has been deleted from this section.	[redacted]
All	Minor formatting and typographical corrections	[redacted]

SYNOPSIS

Clinical Protocol CA204142

Protocol Title: A Phase 2, Multiple Cohort Study of Elotuzumab in Combination with Pomalidomide and Low-Dose Dexamethasone (EPd), and in Combination with Nivolumab (EN), in Patients with Multiple Myeloma Relapsed or Refractory to Prior Treatment with Lenalidomide.

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

Elotuzumab: 10 mg/kg IV - Cycles 1 and 2: Days 1, 8, 15, 22

20 mg/kg IV - Cycle 3 and beyond: Day 1 of each cycle

Pomalidomide: 4 mg PO: Days 1 - 21 of each cycle

Dexamethasone: Days 1, 8, 15, and 22 of each cycle:

- Subjects ≤ 75 years old: Weeks with elotuzumab dosing: 28 mg PO + 8 mg IV and 40 mg PO on non-elotuzumab dosing weeks
- Subjects > 75 years old: Weeks with elotuzumab dosing: 8 mg PO + 8 mg IV and 20 mg PO on non-elotuzumab dosing weeks

Nivolumab:

- Cycles 1 through 4: 240 mg IV Days 1, 15 of each 28-day cycle
- Cycles 5 and beyond: 480 mg IV Day 1 of each 28-day cycle

Study Phase: Phase 2

Research Hypothesis:

Elotuzumab/Pomalidomide/Low-Dose Dexamethasone Cohort (EPd) :

Elotuzumab in combination with pomalidomide and low-dose dexamethasone will prolong progression-free survival (PFS) in subjects with multiple myeloma (MM) who have relapsed or are refractory or intolerant to a lenalidomide-based regimen.

Elotuzumab/Nivolumab Cohort (EN):

The combination of elotuzumab and nivolumab will provide clinical benefit, represented by response rate, in patients with relapsed or refractory multiple myeloma (MM) who have received at least 4 prior lines of therapy including a proteasome inhibitor (PI), immunomodulatory (IMID), and an anti-CD38 antibody.

Objectives:

Primary EPd Cohort Objective:

- To estimate the PFS in patients with MM treated by EPd as second- or third-line regimen after relapse or being refractory or intolerant to a prior lenalidomide based regimen.

Primary EN Cohort Objective:

- To estimate the Objective Response Rate (ORR).

Secondary EPd Objectives

- Estimate the ORR
- Estimate the overall survival (OS) Rate

Secondary EN Cohort Objectives:

- Estimate PFS
- Estimate OS

[redacted]

Study Design:

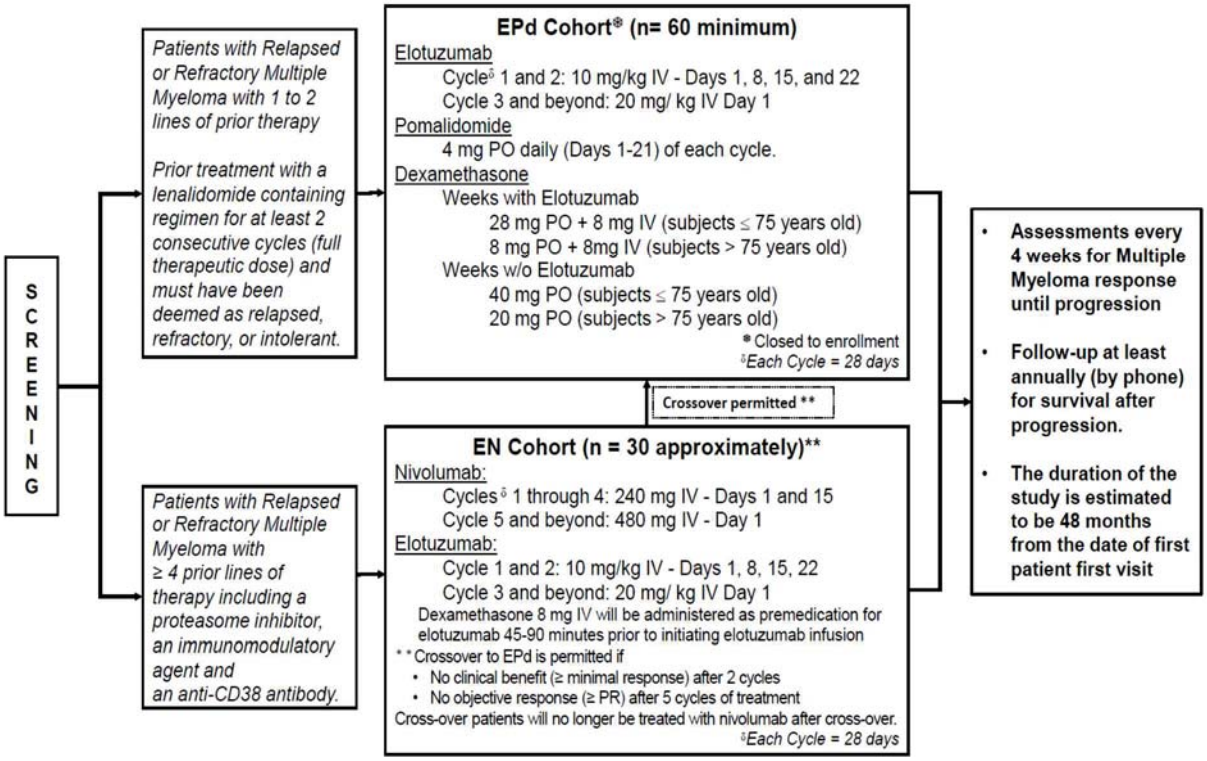
This is a Phase 2, multi-center, open-label, multiple cohort study of elotuzumab in combination with pomalidomide and low dose dexamethasone (EPd Cohort) and elotuzumab in combination with nivolumab (EN Cohort) to assess the safety and efficacy of this combination therapy for treatment of relapsed or refractory MM patients.

Approximately 120 subjects will be screened in this study to treat a minimum of 60 subjects in the EPd Cohort and approximately 30 subjects in the EN Cohort. Screen failure rate is approximately 25%. Per Revised Protocol 03, the EPd cohort is closed to enrollment.

The estimated duration of enrollment is 18 to 24 months, minimum of 24 months follow-up and study duration of about 48 months, estimated from the date first patient, first visit.

If subjects enrolled in the EN cohort do not achieve clinical benefit represented by at least minimal response (≥ MR) after 2 cycles of treatment or do not achieve an objective response (≥ PR) after 5 cycles of treatment, they may cross over to the EPd cohort at Day 1 of the subsequent cycle.

Subjects will continue treatment as long as the subject has clinical benefit from the treatment and do not meet criteria for discontinuation.



Study Population:

Eligible subject must have**:**

a) Documented disease progression per International Myeloma Working Group (IMWG) guidelines during or after their last anti-myeloma therapy

b) As of Amendment 02, this criterion has been moved to criterion 2.g.i for clarity.

c) As of Amendment 02, this criterion has been moved to criterion 2.g.ii for clarity.

d) Measurable disease at screening, based on central laboratory results, defined as 1 or more of the following:

   i) Serum immunoglobulin (Ig)G, IgA, IgM M-protein ≥ 0.5 g/dL

   ii) Urinary M Protein ≥ 200 mg urinary M-protein excretion in a 24 hour collection sample

   iii) Involved serum free light chain (sFLC) ≥ 10 mg/dL provided the FLC ratio is abnormal.

e) Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.

f) As of Amendment 02, this criterion has been moved to criterion 2.g.iii for clarity.

g) for the EPd Cohort:

   i) Subjects must have received at least 1 but no greater than 2 prior lines of therapy (note: induction and stem cell transplants with or without maintenance therapy is considered 1 line of therapy)

   ii) Subjects must have received prior treatment with a lenalidomide-containing regimen for at least 2 consecutive cycles (full therapeutic dose) and must have been deemed as relapsed, refractory, or intolerant. Refractory is defined as progressing on-treatment or within 60 days of the last dose.

   NOTE: lenalidomide-based regimens to which the subject has relapsed or been refractory to is not required to be the most recent regimen received.

iii) Prior elotuzumab exposure is permitted only if subjects fulfill all of the following:

(1). Did not discontinue elotuzumab due to any intolerable drug-related adverse reaction.

(2). Did not participate in a prior elotuzumab clinical trial, regardless of treatment assignment

h) For EN Cohort:

i) Subjects must have received at least 4 prior lines of therapy including a proteasome inhibitor (PI), an immunomodulatory (IMID) agent, and an anti-CD38 antibody.

Subjects not eligible for enrollment include subjects with a) solitary bone or extramedullary plasmacytoma as the only evidence of plasma cells dyscrasia; b) monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM), primary amyloidosis (no active multiple myeloma), Waldenstrom's macroglobulinemia, or POEMS syndrome (plasma cell dyscrasia with poly neuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes); c) 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); d) with Central Nervous System involvement with multiple myeloma.

Study Drug: includes both Investigational [Medicinal] Products (IP/IMP) and Non-investigational [Medicinal] Products (Non-IP/Non-IMP) as listed:

Study Drug for CA204142		
Medication	**Potency**	**IP/Non-IP**
Elotuzumab Powder for Solution for Infusion	400 mg/vial	IP
Dexamethasone Tablets	2 mg and 4 mg and various strengths	Non-IP
Dexamethasone Solution	4 mg/mL, 8 mg/mL and various strengths	Non-IP
Nivolumab for Injection	100 mg/vial	IP
Pomalidomide Capsules	1 mg, 2 mg, 3 mg and 4 mg	IP

Study Assessments:

Assessments for safety and efficacy will be conducted as time points indicated on the time and events schedules included in Section 5. Safety evaluations include assessments of AEs, clinical laboratory tests (hematology, chemistry), vital sign measurements, and physical examination with assessment of ECOG performance score (PS).

Efficacy endpoints will be based on analysis of serum and urine electrophoresis (SPEP and UPEP), sFLC (for those with sFLC disease only), corrected calcium (serum calcium and serum albumin), imaging and bone marrow assessments, all at predefined intervals as specified in Table 5.1-1, Table 5.1-2, Table 5.1-3, Table 5.1-4, Table 5.1-5, and Table 5.1-6. Assessments for SPEP and UPEP will be based on central lab results, whereas assessments of bone marrow, bone lesions, extramedullary plasmacytomas, and corrected calcium will be based on local analysis at the site.

Statistical Considerations:

Sample Size:

EPd Cohort:

Per Revised Protocol 03, the EPd cohort is closed to enrollment. Screening continued until a minimum of 60 patients were enrolled and treated. This total number is based on logistical consideration with statistical properties outlined below.

Under the assumptions that:

- time to progression-free survival is exponentially distributed
- median time of progression-free survival of 11 months among subjects treated with pomalidomide and dexamethasone and will increase to a median of 15 months when elotuzumab is added to the mix
- an increase of 4 months in median corresponds to relative risk ratio of 0.73 (0.0462 monthly risk in the elotuzumab add on and 0.0630 monthly historical risk in the pomalidomide + dexamethasone treated subjects)

Sixty subjects enrolled over a 24-month period are sufficient to detect an increase in median from 11 to 15 months with about 70% power in a one-sided test with a 0.05 significance level.

Assuming a monthly hazard rate of 0.0462, 48 of the 60 treated subjects are expected to have PFS events over a 24 month follow up period

Power is calculated using PASS12 using the one-sample exponential module where the median is mapped to mean by dividing the assumed alternative median by logarithm of 2. The calculated power and event counts are consistent with power and event counts based on one sample log rank test where the number of events is calculated assuming relative risk ratio of 0.73.

EN Cohort

The planned sample size will be approximately 30 treated subjects; screening will continue until a minimum of 30 patients are enrolled and treated. For a 30% observed ORR rate, a sample size of N=30 yields an exact confidence interval of [0.15, 0.49]. These design parameters ensure a lower bound higher than 15 %

Endpoints:

Primary EPd Endpoint:

PFS is defined as the time from first dosing date to the date of the first documented progression per IMWG uniform criteria or death due to any cause, 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 evaluable assessment. Subjects who did not have any on study efficacy assessments and did not die will be censored on the first dosing date.

Subjects who switched to subsequent therapy prior to documented progression will be censored on the date of the last evaluable assessment prior to the initiation of the new therapy.

Primary EN Endpoints

ORR is defined as proportion of subjects with best overall response of partial response (PR) or better. Response will be determined per IMWG uniform criteria.

Secondary EPd Endpoints

- Objective Response Rate (ORR) is defined as the proportion of subjects with a best overall response of partial response (PR) or better
- Overall Survival (OS) is defined as the time from first dosing date to the date of death from any cause. A subject who has not died will be censored at last known date alive.

Secondary EN Endpoints:

- PFS is defined as the time from first dosing date to the date of the first documented progression per IMWG uniform criteria or death due to any cause, whichever occurs first. Subjects who die without a reported prior progression will be considered to have progressed on the date of their death.
- OS is defined as the time from first dosing date to the date of death from any cause. A subject who has not died will be censored at last known date alive.

[redacted]

Analyses

Demographics and Baseline Characteristics: The demographic and baseline characteristics of patients in the safety analysis set will be presented.

Efficacy Analyses: The efficacy endpoints, progression free survival and objective response rate (ORR), will be defined using the International Myeloma Working Group criteria. Responses will be assessed at every treatment cycle using central laboratory test results on myeloma urine and serum, local laboratory bone marrow aspiration test, and if needed bone marrow and skeletal survey results and CT/MRI assessments. Objective responses will include stringent complete response, complete response, very good partial response and partial responses. The objective response rate and its 95% confidence interval (CI) using the Clopper-Pearson estimation procedure will be reported. Progression free survival and overall survival will be plotted using Kaplan-Meier estimates, and if estimable, median and its 95% CI will be reported. [redacted]

[redacted]

For EPd cohort, the primary analysis of PFS will be conducted when 48 progression events have been observed.

For EN cohort, the primary analyses for ORR will be conducted when enrollment in the EN cohort is complete and all enrolled patients treated with the combination have received at least 3 cycles of treatment.

[redacted]

Safety Analyses

Safety assessments will be performed prior, during and between dosing, and up to 100 days after last treatment in the EN cohort, 60 days after the last dose in the EPd cohort and for subjects in the EN cohort who cross-over to the EPd cohort but discontinue treatment within 2 cycles of EPd treatment safety assessments will be performed up to 100 days after the last dose of nivolumab. The frequency, severity, relationship to combination of drug treatment, seriousness, and outcomes of adverse events (AEs) will be reported for the full safety analysis set. AE severity will be graded according to the NCI Common Terminology Criteria for Adverse Events 3.0. Results of targeted physical examinations prior to each dosing cycle will be presented. Summary statistics on vital signs at screening, pre-infusion, 30 minutes after the start of infusion, at end of infusion and 30 minutes after the completion of infusion will be reported for Cycle 1 and pre-infusion for Cycle 2 and beyond. Concomitant medications, SAEs, and performance status prior to dosing will be presented. The safety analysis set will be used for reporting safety /adverse events.

Biomarker Analyses

No biomarker analysis is planned for the EPd Cohort. In the EN Cohort, the potential association between PD-L1 expression and clinical efficacy measures, such as overall response, 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.

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1.2 Research Hypotheses

1.2.1 EPd Cohort

Elotuzumab in combination with pomalidomide and low-dose dexamethasone will prolong PFS in subjects with MM who have relapsed or are refractory or intolerant to a lenalidomide-based regimen.

1.2.2 EN Cohort

The combination of elotuzumab and nivolumab will provide clinical benefit, represented by response rate, in patients with relapsed or refractory multiple myeloma (MM) who have received at least 4 prior lines of therapy including a proteasome inhibitor (PI), an immunomodulatory (IMID) agent and an anti-CD38 antibody.

1.3 Objectives(s)

1.3.1 Primary Objectives

1.3.1.1 EPd Cohort:

- To estimate the PFS in patients with MM treated by EPd as second- or third-line regimen after relapse or being refractory or intolerant to a prior lenalidomide-based regimen.

1.3.1.2 EN Cohort:

- To estimate the ORR.

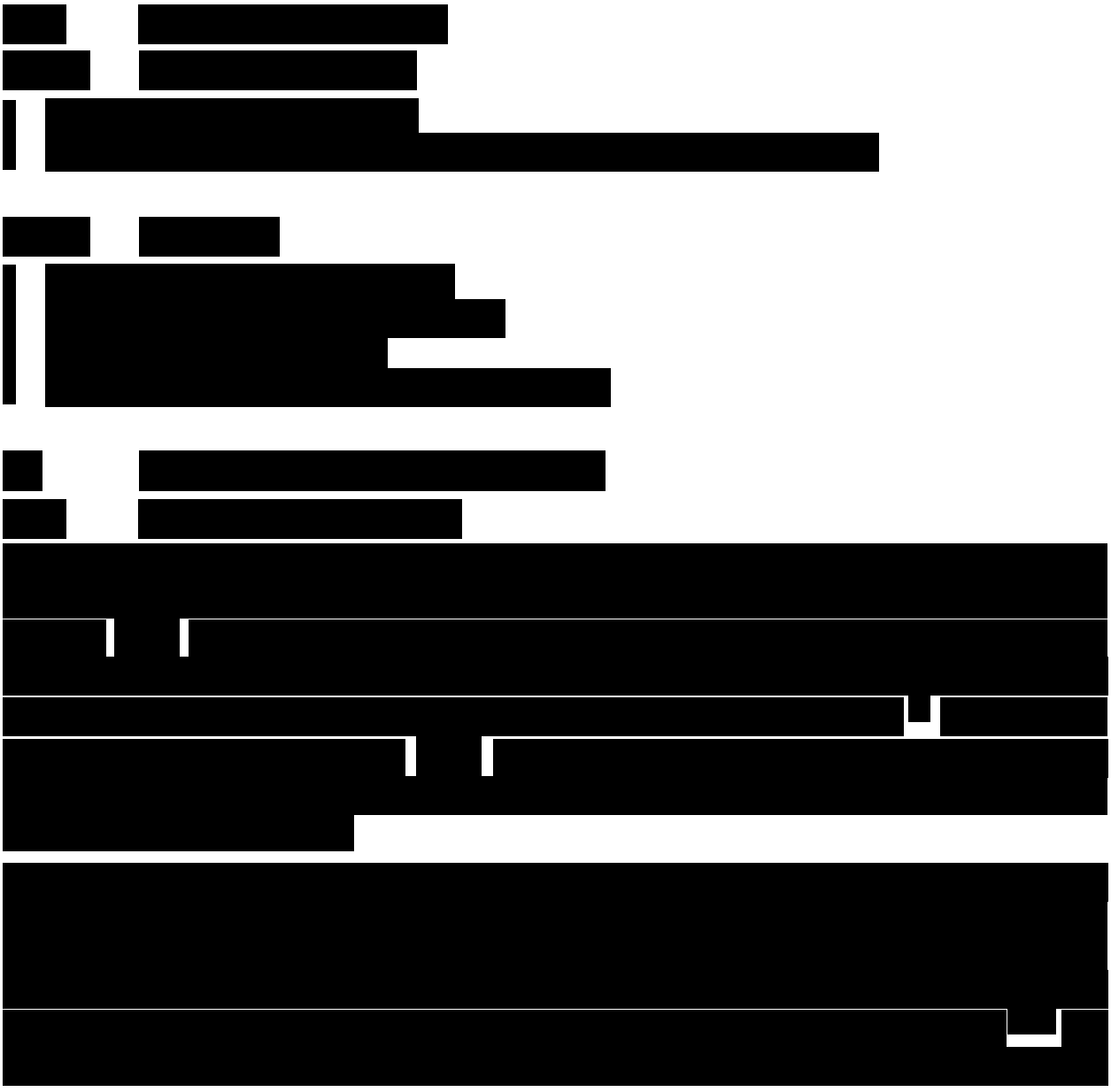
1.3.2 Secondary Objectives

1.3.2.1 EPd Cohort:

- Estimate the ORR
- Estimate OS Rate

1.3.2.2 EN Cohort:

- Estimate PFS
- Estimate OS



1.5 Overall Risk/Benefit Assessment

The American Cancer Society has estimated 30,330 new MM cases in the US in 2016, with an estimated 12,650 deaths.[1] While recent advances in the use of high-dose chemotherapy, targeted therapeutics, and stem cell transplantation have improved overall and event-free survival, the majority of patients with myeloma will relapse and disease progression is expected for all but a small percentage.[5] The subjects enrolled in the EPd trial will receive an anti-myeloma regimen of pomalidomide + dexamethasone which demonstrated improvements in PFS, OS, and overall response in patients with refractory or relapsed and refractory multiple myeloma, including patients with disease refractory to both bortezomib and lenalidomide.[29] Pomalidomide has gained U.S. FDA accelerated approval and EMA approval in this population of MM patients at a dose of 4 mg, which is the dose being used in this trial.

Since pomalidomide may enhance the activity of NK cells, which are central to the main biological activity of elotuzumab, combining both drugs is likely to enhance elotuzumab mediated ADCC towards primary myeloma cells in a similar way to that observed with lenalidomide. The expectation is that subjects in this trial will derive clinical benefit.

Pomalidomide is an analogue of thalidomide, which is known to cause severe life-threatening human birth defects. Because of this potential toxicity and to avoid fetal exposure, pomalidomide is only available under a special restricted distribution program Pomalyst® REMS (Section 4.3.3). Subjects may also follow Pomalidomide Pregnancy Risk Prevention Plan (Appendix 6) where applicable. All investigators and subjects must fully comply with and participate in the distribution program in order to participate in this trial.

Elotuzumab as monotherapy or in combination with immunomodulatory agents such as thalidomide or lenalidomide is well tolerated. Safety data from an interim analysis of the ongoing randomized phase 3 study of lenalidomide and dexamethasone with or without elotuzumab in patients with relapsed or refractory multiple myeloma (Eloquent 2) has shown that elotuzumab was well tolerated in combination with lenalidomide/dexamethasone, with minimal incremental toxicity and no new safety signals. The safety profile of elotuzumab was consistent across IMiD combination studies (thalidomide and lenalidomide). As pomalidomide is an analogue of thalidomide, a similar safety profile is expected when pomalidomide + dexamethasone is combined with elotuzumab. Key elotuzumab adverse events have been infusion related events.[14] These have all been managed by medications and resolved in less than 24 hours. The frequency and intensity of infusion related adverse events has been mitigated with premedications, including corticosteroids, histamine-1 and -2 antagonists, and acetaminophen. Guidelines for the management of infusion reactions are also provided in this protocol (See Section 4.5.5).

Nivolumab is approved in multiple solid tumor indications and hematologic malignancies (eg, classical Hodgkin lymphoma) based on its favorable benefit/risk assessment. In hematological malignancies including multiple myeloma, nivolumab monotherapy was generally well tolerated and toxicity profile was similar to that observed in solid tumors. Nivolumab has the potential for clinically relevant unique AEs potentially caused by an inflammatory mechanism. These include pulmonary toxicity, hepatotoxicity, diarrhea/colitis, endocrinopathies, and nephrotoxicity. To date, these unique AEs have been manageable with frequent monitoring, prompt diagnosis, and initiation of corticosteroids, dose interruption, and adequate supportive care. The management algorithms of the immune-related AEs are included in Appendix 7.

Because nivolumab and elotuzumab have non-overlapping toxicity profiles, the combination of both drugs is not expected to increase toxicities.

Elotuzumab combination with nivolumab is an experimental therapy and it is possible that unforeseen or unanticipated adverse events may occur although both agents have been evaluated separately in combination with other agents in multiple myeloma and have known toxicity profiles. In order to minimize the overall risks to participating subjects, the protocol has inclusion-exclusion criteria appropriate to the population, and specific follow-up safety assessments. Adverse events and serious adverse events will be reviewed on an ongoing basis by the Medical Monitor and the Sponsor's pharmacovigilance group to look for trends and safety concerns. Stopping rules for unexpected toxicity have been incorporated into the protocol. Treatment options in this later line relapsed/refractory myeloma setting are limited and it is possible that this combination may provide clinical benefit to patients.

The overall assessment of risk/benefit supports the evaluation of elotuzumab in combination with pomalidomide and dexamethasone in multiple myeloma and also the combination of elotuzumab with nivolumab in the later line relapsed/refractory multiple myeloma setting.

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 Harmonisation (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 (as per country guidelines) 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.

Subjects unable to give their written consent (eg, stroke or subjects with or severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this subject become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a subject who is unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

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 2, multi-center, open-label, multiple cohort study of elotuzumab in combination with pomalidomide and low-dose dexamethasone (EPd Cohort) and elotuzumab in combination with nivolumab (EN Cohort) to assess the safety and efficacy of these combination therapies for treatment of relapsed or refractory MM patients.

In the EPd Cohort, subjects will receive treatment with elotuzumab in combination with pomalidomide and low-dose dexamethasone in a 28 day cycle. Subjects will receive 10 mg/kg IV elotuzumab on Days 1, 8, 15, and 22 of Cycles 1 and 2. Starting with Cycle 3, subjects will receive 20 mg/kg on Day 1.

As of Amendment 02, subjects will also be enrolled in the EN cohort to receive a combination of elotuzumab and nivolumab in a 28-day cycle. EN subjects will receive nivolumab 240 mg IV on Days 1 and 15 for Cycles 1-4. At Cycle 5 and beyond, subjects will receive 480 mg IV on Day 1. Subjects will also receive elotuzumab 10 mg/kg on Days 1, 8, 15, and 22 of Cycles 1 and 2. At Cycle 3 and beyond, subjects will receive 20 mg/kg of elotuzumab IV on Day 1. If subjects do not achieve clinical benefit represented by at least minimal response (≥ MR) after 2 cycles of treatment or do not achieve an objective response (≥ PR) after 5 cycles of treatment, they may cross over to the EPd cohort at Day 1 of the subsequent cycles if they also meet the eligibility criteria for cross-over specified in Section 3.3.4.

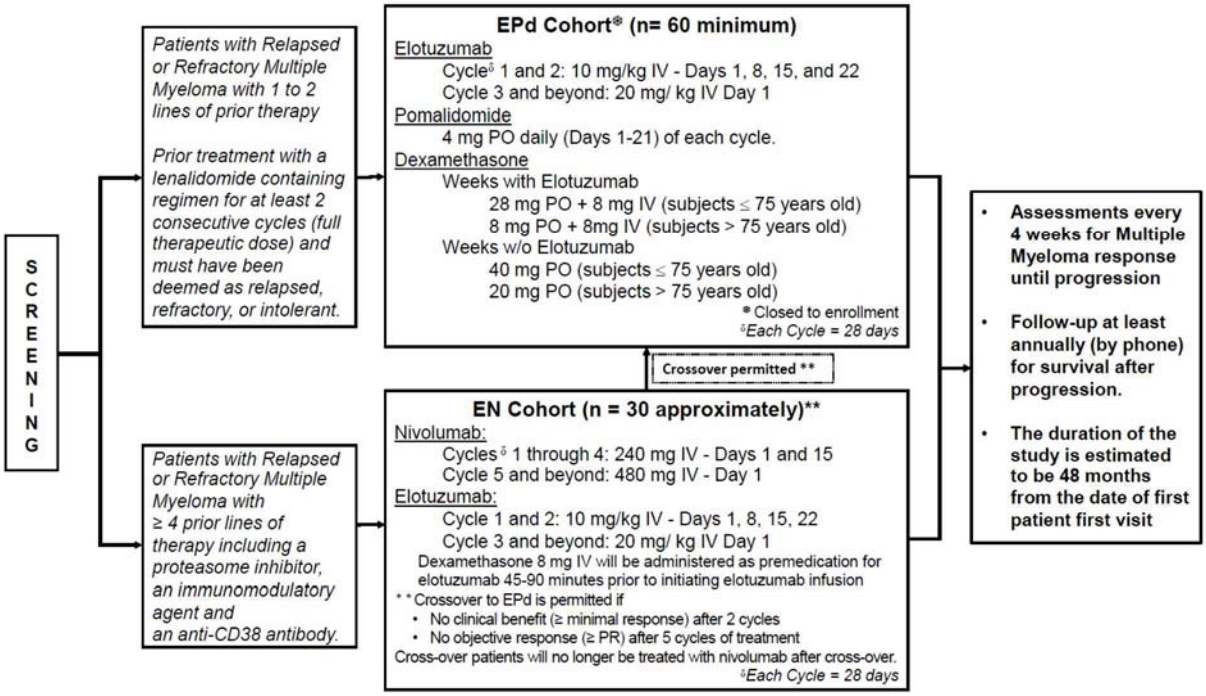
Subjects will continue treatment as long as the subject has clinical benefit from the treatment and do not meet criteria for discontinuation.

All subjects will be assessed for safety and response as presented in the Time and Event Tables in Section 5. Subjects who are discontinued from further study treatment for reasons other than progression will be followed for disease progression. Following disease progression, subjects will be followed at least annually for survival.

Approximately 120 subjects will be screened in this study. A minimum of 60 subjects will be treated in the EPd Cohort. Approximately 30 subjects will be treated in the EN Cohort. The estimated duration of enrollment is 18 to 24 months, and the duration of the study is estimated at 48 months from the date of first patient, first visit. Per Revised Protocol 03, the EPd cohort is closed for enrollment.

The study design schematic is presented in Figure 3.1-1.

Figure 3.1-1: Study Design Schematic



3.2 Post Study Access to Therapy

At the conclusion of the study, subjects who continue to demonstrate clinical benefit are eligible to receive BMS supplied 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 BMS supplied 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) Subject is, in the investigator's opinion, willing and able to comply with the protocol requirements.

b) Subject has given voluntary written informed consent before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to their future medical care.

2. Target Population

a) All subjects must have documented disease progression per IMWG (Appendix 4) criteria during or after their last anti-myeloma therapy.

b) As of Amendment 02, this criterion has been moved to criterion 2.i.i for clarity.

c) As of Amendment 02, this criterion has been moved to criterion 2.i.ii for clarity.

d) Per Amendment 1, this criterion is no longer applicable. Specifications previously listed in criterion d) have been included in the revised criterion c) above.

e) Measurable disease at screening, based on central laboratory results, defined as one or more of the following:

   i) Serum IgG, IgA, IgM M-protein ≥ 0.5 g/dL

   ii) Urinary M-Protein ≥ 200 mg urinary M-protein excretion in a 24 hour collection sample

   iii) Involved serum free light chain (sFLC) ≥ 10 mg/dL provided the FLC ratio is abnormal.

f) ECOG Performance Status ≤ 2 (Appendix 2).

g) Subject Re-enrollment: This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, has not been treated). If re-enrolled, the subject must be re-consented.

h) As of Amendment 02, this criterion has been moved to criterion 2.i.iii for clarity.

i) for the EPd Cohort:

   i) Subjects must have received at least 1 but no greater than 2 prior lines of therapy (note: induction and stem cell transplants with or without maintenance therapy is considered 1 line of therapy)

   ii) Subjects must have received prior treatment with a lenalidomide-containing regimen for at least 2 consecutive cycles (full therapeutic dose) and must have been deemed as relapsed, refractory, or intolerant. Refractory is defined as progressing on-treatment or within 60 days of the last dose.[30]

   NOTE: lenalidomide-based regimens to which the subject has relapsed or been refractory to is not required to be the most recent regimen received.

   iii) Prior elotuzumab exposure is permitted only if subjects fulfill all of the following:

      (1). Did not discontinue elotuzumab due to any intolerable drug-related adverse reaction.

      (2). Did not participate in a prior elotuzumab clinical trial, regardless of treatment assignment

j) For EN Cohort:

   i) Subjects must have received at least 4 prior lines of therapy including a proteasome inhibitor (PI), an immunomodulatory (IMID) agent, and an anti-CD38 antibody.

3. Age and Reproductive Status

a) Males and Females, at least 18 years or legal age of consent per local regulations

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

c) Women must not be breastfeeding

d) WOCBP must agree to follow instructions for method(s) of contraception for 1 month (4 weeks) before the start of treatment with study drugs, for the duration of treatment with study drugs, and for a total of 5 months post-treatment completion.

e) Males who are sexually active with WOCBP must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking pomalidomide and for up to 28 days after discontinuing pomalidomide, even if they have undergone a successful vasectomy. Male patients must not donate sperm.

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

g) All subjects must be willing and able to comply with the local pomalidomide risk management program or the Pomalidomide Pregnancy Risk Prevention Plan

h) All subjects must agree not to share study medication.

i) Male subjects receiving elotuzumab or nivolumab must also agree to follow instructions for method(s) of contraception for 1 month (4 weeks) before the start of treatment with study drugs, for the duration of treatment with study drugs, and for a total of 7 months post-treatment completion.

j) Subjects must be willing to refrain from blood donations during study drug therapy and for 90 days after therapy.

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 below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena® by WOCBP subject or male subject's WOCBP partner. Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug
- IUDs, such as ParaGard®
- Tubal ligation
- Vasectomy
- Complete Abstinence*

*Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

LESS EFFECTIVE METHODS OF CONTRACEPTION

- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge
- Male Condom without spermicide
- Progestin only pills by WOCBP subject or male subject's WOCBP partner
- Female Condom*
- * A male and female condom must not be used together

3.3.2 Exclusion Criteria

1. **Target Disease Exceptions: EN and EPd Cohorts**
   a) Subjects with solitary bone or extramedullary plasmacytoma as the only evidence of plasma cells dyscrasia.
   b) Subjects with monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM), primary amyloidosis (no active multiple myeloma), Waldenstrom's macroglobulinemia, or POEMS syndrome (plasma cell dyscrasia with poly neuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)
   c) Subjects with 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 2×10^9/L)
   d) Subjects with Central Nervous System involvement with multiple myeloma
2. **Medical History and Concurrent Diseases** - for both cohorts unless otherwise noted.
   a) Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the patient from signing the informed consent form
   b) Any serious concurrent medical conditions that may make the patient non-evaluable or put the patient's safety at risk
   c) Active infection that requires parenteral anti-infective treatment >14 days
   d) Unable to tolerate thromboembolic prophylaxis while on the study
   e) Severe hypersensitivity reaction to prior IMiD (thalidomide or lenalidomide)
   f) Grade > 2 peripheral neuropathy (per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v3.0)
   g) Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic infection.
   h) Known HIV infection or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at sites where mandated locally
   i) Prior or concurrent malignancy, except for the following:
      i) Adequately treated basal cell or squamous cell skin cancer or in-situ carcinoma.
      ii) Any other cancer from which the subject has been disease free for > 3 years prior to study entry.

j) Additionally for EN Cohort:

i) 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

ii) Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of initiation of study drug. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease

3. Prior therapy or surgery

a) For EPd Cohort

i) Prior treatment with pomalidomide

ii) Prior participation in an elotuzumab clinical trial regardless of treatment assignment.

iii) Prior discontinuation of treatment with elotuzumab due to intolerable drug-related adverse reactions

iv) Use of any anti-myeloma drug therapy within 14 days of the initiation of study drug treatment or use of any experimental drug therapy within 28 days of the initiation of study drug treatment

v) Treatment with melphalan within 4 weeks of the first dose of study drug

vi) Treatment with corticosteroids (other than the dexamethasone of anti-myeloma regimens) within 3 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)

vii) Prior autologous stem cell transplant within 12 weeks of the first dose of study drug

viii) Prior allogeneic stem cell transplant except subjects who have completed the stem cell transplant > 12 months prior to first dose of study drug, have no history of graft versus host disease, and are not on systemic immunosuppressive therapy

ix) 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 dose of study drug.

b) For EN Cohort

i) Prior treatment with elotuzumab or nivolumab (or any PD-1 or PD-L1 inhibitor).

ii) Use of any anti-myeloma drug therapy, within 14 days of the initiation of study drug treatment. Bisphosphonate use permitted if initiated prior to first dose of study medication

iii) All prior drug-related AEs should have resolved or returned to baseline for the subject to be eligible

iv) Prior autologous stem cell transplant within 12 weeks of the first dose of study drug

v) Prior allogeneic stem cell transplant or graft versus host disease (GVHD) within 12 months of the first dose of study drug, or subjects on topical or systemic immunosuppressive therapy for GVHD

vi) 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

vii) 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 dose of study drug. (Kyphoplasty is not considered major surgery); subjects should have been fully recovered from any surgical related toxicities

4. Physical and Laboratory Test Findings - For both cohorts:

- Absolute neutrophil count < 1 x 10^9/L (without growth factor support within 1 week)
- Platelets < 75 x 10^9/L (< 30 x 10^9/L if ≥ 50% of bone marrow nucleated cells were plasma cells) (without transfusion support within 3 days)
- Creatinine clearance < 30 ml/min according to the Cockroft-Gault formula:
  - Female CrCl = $\frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dl}}$
  - Male CrCl = $\frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dl}}$
- Total bilirubin ≥ 2 x ULN (≥ 3 x ULN if Gilbert's syndrome)
- AST or ALT ≥ 3x ULN

5. Allergies and Adverse Drug Reaction (For both Cohorts)

a) Known severe hypersensitivity or allergy to dexamethasone, any excipients in elotuzumab, formulation or recombinant protein, or any monoclonal antibody

6. Other Exclusion Criteria (For both Cohorts)

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

3.3.3 Women of Childbearing Potential

A Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and 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 > 40mIU/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 judgment in checking serum FSH levels. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal:

- 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.

3.3.4 Eligibility Criteria for EN Patients to Cross-over to EPd cohort.

Crossover to EPd is permitted if:

- No clinical benefit (≥ minimal response) after 2 cycles.
- No objective response (≥ PR) after 5 cycles of treatment.

EN patients who cross-over will no longer be treated with nivolumab after the cross-over to the EPd cohort. Re-consent is not required for EN patients who cross-over to treatment with EPd.

EN patients who do not cross-over can continue treatment with EN until discontinuation criteria are met, as specified in Section 3.5.

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.

[redacted]

[redacted]

[redacted]

3.5 Discontinuation of Subjects following any Treatment with Study Drug

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

- Subject's request to stop study treatment
- Any clinical adverse event (AE), laboratory abnormality 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
- Termination of the study by Bristol-Myers Squibb (BMS) or meeting the criteria for stopping rules for cohort(Section 4.5.10).
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Pregnancy (Subjects must discontinue the study drugs.
- Progressive Disease (Appendix 4)
- Subjects who receive any non-protocol specified systemic anti-myeloma therapy before documented progression will be discontinued from all study treatment (including pomalidomide/dexamethasone); however, tumor assessments will continue at 4 week intervals until documented progression.
- Subjects experiencing a Grade 4 infusion reaction related to elotuzumab must discontinue elotuzumab (refer to the Grade 4 Infusion Reaction subsection presented in Section 4.5.5) Subjects may continue pomalidomide and dexamethasone treatment.
- Subjects experiencing a Grade 3 or 4 infusion reaction related to nivolumab must discontinue nivolumab (only).
- Subjects experiencing angioedema, Grade 4 rash, exfoliative or bullous rash, Stevens-Johnson syndrome, or toxic epidermal necrolysis related to pomalidomide must discontinue pomalidomide. Subjects may continue elotuzumab and dexamethasone.
- Subjects experiencing a 56 day delay in all study drugs (elotuzumab, nivolumab, pomalidomide, and dexamethasone) due to an adverse event(s) related to study treatment must be discontinued from study drug. 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 medical monitor.

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event, and treatment with the IMPs would immediately be stopped. In most cases, the study drug will be permanently discontinued in an appropriate manner. Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy. If the investigator

determines a possible favorable benefit/risk ratio that warrants continuation of study drug (ie, allowing restart of study drug if the patient choses to terminate the pregnancy), a discussion between the investigator and the BMS Medical Monitor/designee must occur so that permission can be granted.

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

If study drug is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate case report form (CRF/eCRF) page.

3.6 Post Study Drug Study Follow up

In this study, PFS is a key endpoint of the study. Post study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study drug must continue to be followed for collection of PFS. Subjects who discontinue study therapy must also continue to be followed for overall survival data in line with Section 5 until death or the conclusion of the study.

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/eCRF 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. STUDY DRUG

Study drug includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) and are listed in Table 4.-1.

Table 4.-1: Study Drugs for CA204142

Product Description / Class and Dosage Form	Potency	IMP/Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
Elotuzumab Powder for Solution for Infusion	300 mg/vial or 400 mg/vial	IMP	Open Label	Vial	Refer to the label on the container and/or the pharmacy manual.
Nivolumab Solution for Injection	100 mg (10 mg/mL)	IMP	Open label	Vial	Refer to the label on the container and/or the pharmacy manual.
Dexamethasone Tablets	2 mg and 4 mg and various strengths	Non-IMP	Open-label	Various packing configurations	Refer to label on container or package insert / summary of product characteristics
Dexamethasone Solution	4 mg/mL, 8 mg/mL and various strengths	Non-IMP	Open-label	Various packing configurations	Refer to label on container or package insert / summary of product characteristics
Pomalidomide Capsules	1 mg, 2 mg, 3 mg and 4 mg	IMP	Open label	Various packing configurations	Refer to label on container or package insert

Pomalidomide (Pomalyst®), Dexamethasone tablets and solution for IV infusion will be obtained by the investigating site's standard prescribing procedures.

4.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined 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.

4.2 Non-investigational 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 non-investigational products.

In this protocol, non-investigational product(s) are: dexamethasone tablets and concentrate for solution for IV infusion, or products used for Elotuzumab premedication Section 4.5.3.1 or thromboprophylaxis (Section 3.4.1).

4.3 Storage 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 BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

Study drug not supplied by BMS will be stored in accordance with the package insert.

Investigational product documentation (whether supplied by BMS or not) 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).

Procedures for proper handling and disposal of anticancer drugs should be considered.

The investigator or designee accepts responsibility for documenting traceability and study drug integrity in accordance with requirements applicable under law and the standard operating procedures (SOPs)/standards of the sourcing pharmacy. These records should include:

- label identification number or batch number
- the amount dispensed to and returned by each subject, including unique subject identifiers dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

4.3.1 Elotuzumab

The lyophilized elotuzumab drug product should be stored at 2° to 8°C. Before administration the drug product must be reconstituted with Sterile Water for Injection, USP, and then further diluted in 0.9% sodium chloride normal saline, United States Pharmacopoeia (USP), as per the instructions in Appendix 3. The dose of elotuzumab to be administered to a subject will be calculated by multiplying the subject's weight (kg) by 10 or 20 mg/kg. The subject's predose weight on Day 1 of each cycle will be used to calculate the dose for each cycle. The screening weight can be used for the Cycle 1 dose calculation. Each dose should be infused as per instructions in Appendix 3. The infusion start and stop time will be recorded in the CRF/eCRF. If the infusion is stopped mid-session for any reason, the stop/start time must be recorded together with an explanation. Please refer to the pharmacy manual for detailed guidance on storage, preparation and administration.

4.3.2 Nivolumab

Nivolumab will be administered at a dose of 240 mg as an intravenous infusion over 30 minutes every 2 weeks (Days 1 and 15 of each 28 day cycle) during Cycles 1 through 4. Starting Cycle 5 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 for guidelines on drug preparation and administration. Flush the intravenous line at the end of infusion.

Nivolumab vials must be stored at a temperature of 2°to 8°C and should be protected from light and freezing. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

4.3.3 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.

Because of this potential toxicity and to avoid fetal exposure to pomalidomide, pomalidomide is only available under a special restricted distribution program. This program is called Pomalyst® REMS. Pomalidomide must only be dispensed to subjects who meet all the conditions of Pomalyst® REMS. Subjects who have the potential of pregnancy in Pomalyst® REMS must be instructed about contraception and undergo the scheduled pregnancy tests.

Please see the US package insert for additional information for prescribing to female subjects and male subjects about this restricted distribution program.

Subjects should not break, chew or open the capsules. Pomalidomide should be taken without food (at least 2 hours before or 2 hours after a meal). Only enough pomalidomide for one cycle of therapy will be supplied to the patient each cycle in accordance with Pomalyst® REMS.

4.3.4 Dexamethasone

Dexamethasone tablets and solution for IV infusion is considered NIMP for this study and will not be provided by the sponsor. It will be obtained by the investigating sites standard prescribing procedures. Marketed product will be utilized for this study and should be stored in accordance with the package insert.

4.4 Method of Assigning Subject Identification

After the subject's eligibility is established and 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 following information is required for subject enrollment:

- Date of Birth
- Gender
- Site number
- Date that informed consent was obtained

Instructions on the use of IVRS will be provided in a separate document.

4.5 Selection and Timing of Dose for Each Subject

Table 4.5-1: Treatment Schedule for EPd Cohort and Cross over Patients from EN Cohort

Cycle	Cycle 1				Cycle 2				Cycle 3 and beyond[b]			
Day	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**
Elotuzumab	10 mg/kg	10 mg/kg	10 mg/kg	10 mg/kg	10 mg/kg	10 mg/kg	10 mg/kg	10 mg/kg	20 mg/kg			
Dexamethasone[a]	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓
Pomalidomide	Days 1-21				Days 1-21				Days 1-21			

[a] See Table 4.5.2-1 for the dose of dexamethasone.

[b] Patients who cross over from the EN cohort will follow the treatment schedule for Cycle 3 and beyond

Table 4.5-2: Treatment Schedule for the EN Cohort

Cycle	Cycles 1 and 2				Cycles 3 and 4				Cycle 5 and beyond			
Day	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**
Elotuzumab	10 mg/kg	10 mg/kg	10 mg/kg	10 mg/kg	20 mg/kg				20 mg/kg			
Nivolumab	240 mg		240 mg		240 mg		240 mg		480 mg			

See Table 4.5.2-2 for dexamethasone IV dose administered as pre-medication for elotuzumab

4.5.1 Pomalidomide

Pomalidomide 4 mg will be administered orally once daily for the first 3 weeks of a 4-week cycle. Pomalidomide should be taken without food (at least 2 hours before or 2 hours after a meal). Subjects should not break, chew or open the capsules.

On the days of elotuzumab administration, the dose of pomalidomide is to be administered at least 2 hours after completion of elotuzumab dosing.

Pomalidomide delay 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

Females of reproductive potential must have negative pregnancy testing and use contraception methods before initiating pomalidomide.

4.5.2 Dexamethasone

Dexamethasone for subjects in the EPd cohort will be administered as indicated in Table 4.5.2-1.

Table 4.5.2-1: Dexamethasone Dosing, EPd Cohort

Age	Day	1	8	15	22
Cycles 1 and 2					
≤ 75 years old	Dexamethasone (mg)	28 mg PO + 8 mg IV[a,b]	28 mg PO + 8 mg IV[a,b]	28 mg PO + 8 mg IV[a,b]	28 mg PO + 8 mg IV[a,b]
> 75 years old	Dexamethasone (mg)	8 mg PO + 8 mg IV[a,b]	8 mg PO + 8 mg IV[a,b]	8 mg PO + 8 mg IV[a,b]	8 mg PO + 8 mg IV[a,b]
Cycles 3 and beyond					
≤ 75 years old	Dexamethasone (mg)	28 mg PO + 8 mg IV[a,b]	40 mg PO per week[c]	40 mg PO per week[c]	40 mg PO per week[c]
> 75 years old	Dexamethasone (mg)	8 mg PO + 8 mg IV[a,b]	20 mg PO per week[c]	20 mg PO per week[c]	20 mg PO per week[c]

[a] On days of elotuzumab, infusion dexamethasone will be administered as a split dose of:

28 mg PO, for subjects ≤ 75 years old **or** 8 mg PO for subjects > 75 years old (between 3 - 24 hours before the start of elotuzumab infusion)

AND

8 mg IV (on the day of elotuzumab infusion at least 45 minutes before the start of infusion)

[b] If elotuzumab dosing is skipped or discontinued, dexamethasone will be administered orally as in days without elotuzumab.

[c] Note the dexamethasone dose, as elotuzumab is not given on Days 8, 15 and 22 of cycle 3 and beyond.

At the investigator's discretion, the oral dexamethasone may be given as a split dose over 2 consecutive days. Dexamethasone delay should be performed as clinically indicated at the discretion of the investigator.

Dexamethasone for subjects in the EN cohort will be administered as indicated in Table 4.5.2-2.

Table 4.5.2-2: Dexamethasone Dosing: EN Cohort

Age	Day	1	8	15	22
Cycles 1 and 2					
All subjects	Dexamethasone (mg)	8 mg IV[a,b]	8 mg IV[a,b]	8 mg IV[a,b]	8 mg IV[a,b]
Cycles 3 and beyond					
All subjects	Dexamethasone (mg)	8 mg IV[a,b]	--	--	--

[a] On days of elotuzumab, dexamethasone will be administered as a premedication at dose of 8 mg IV at least 45 minutes before the start of infusion)

[b] If elotuzumab dosing is skipped or discontinued, dexamethasone will be not be administered.

4.5.3 Elotuzumab

Elotuzumab will be administered intravenously at a dose of 10 mg/kg weekly (Days 1, 8, 15, and 22 of a 4-week cycle) of the first 2 cycles and starting Cycle 3, elotuzumab will be administered intravenously at a dose of 20 mg/kg of Day 1 of each cycle. A window of -1 to + 3 days is permitted in Cycles 1 and 2.

In Cycle 1 and 2, an elotuzumab dose that falls outside of the pre-specified window must be skipped.

In Cycles 3 and beyond, elotuzumab dosing may be delayed for up to 1 week as clinically indicated. If unable to administer within 1 week, then the dose should be skipped and resumption of the elotuzumab continues per the protocol defined schedule.

4.5.3.1 Premedication Before Elotuzumab in Subjects Without a Prior Infusion Reaction

On weeks of elotuzumab infusion, the dexamethasone dose for the EPd cohort will be split into a PO and IV administration (described in Section 4.5.2), which will also serve as premedication for elotuzumab.

Intravenous and PO dexamethasone doses are calculated to provide a total dose that is bioequivalent to an oral dose of 40 mg (subjects who are ≤ 75 years old) or 20 mg (in subjects who are > 75 years old). (Dexamethasone 8 mg IV is approximately bioequivalent to 11 mg PO).

For the EN cohort, dexamethasone will still be administered as a premedication for elotuzumab at a dose of 8 mg IV 45-90 minutes prior to initiating the elotuzumab infusion.

In addition, the following must also be administered 45 to 90 minutes before initiating the elotuzumab:

- H1 blocker: diphenhydramine (25 - 50 mg PO or IV) or equivalent
- H2 blocker: ranitidine (50 mg IV) or equivalent (eg, 150 mg PO)
- Acetaminophen (650 - 1000 mg PO)

4.5.3.2 Elotuzumab Premedication Regimen in Subjects With a Prior Infusion Reaction

To be re-treated with elotuzumab, subjects with a prior infusion reaction must receive H1, H2 blockers and acetaminophen at maximum doses specified (ie, 50 mg diphenhydramine, 50 mg ranitidine [or equivalent], and 650-1000 mg acetaminophen) 45 to 90 minutes before initiating the elotuzumab.

Recommended dexamethasone dosing is summarized in Table 4.5.3.2-1.

Decisions to use more aggressive premedication schemes in subjects with prior Grade 1 infusion reactions or only one prior Grade 2 infusion reaction must be approved by the Medical Monitor.

Table 4.5.3.2-1: Corticosteroid Premedication

	For Subjects ≤ 75 years old	For Subjects > 75 years old
Prior Infusion Reaction	Corticosteroid Premedication[a] Before Elotuzumab	
None or Only Grade 1 infusion reaction[b]	28 mg po dexamethasone (3 - 24 hrs before elotuzumab) AND 8 mg IV dexamethasone at least 45 min before elotuzumab	8 mg po dexamethasone (3 - 24 hrs before elotuzumab) AND 8 mg IV dexamethasone at least 45 min before elotuzumab
Prior Grade 2 infusion reaction[c]	28 mg po dexamethasone (3 - 24 hrs before elotuzumab) AND 10 mg IV dexamethasone at least 45 min before elotuzumab	8 mg po dexamethasone (3 - 24 hrs before elotuzumab) AND 10 mg IV dexamethasone at least 45 min before elotuzumab
Prior Grade 3 or recurrent Grade 2 infusion reaction	8 mg oral dexamethasone (12 - 24 hrs before elotuzumab) AND 8 mg oral dexamethasone (at least 3 hrs before elotuzumab, on the same day as the infusion) AND 18 mg IV dexamethasone at least 45 min before elotuzumab	2 mg oral dexamethasone (12 - 24 hrs before elotuzumab) AND 2 mg oral dexamethasone (at least 3 hrs before elotuzumab, on the same day as the infusion) AND 12 mg IV dexamethasone at least 45 min before elotuzumab

For prior infusion reactions, use maximum doses H1, H2 blockers and acetaminophen as described in Section 4.5.3.1.

[a] At the discretion of the investigator, the oral dexamethasone component may be given as a split dose 12-24 and 3 hours before elotuzumab.

[b] Subjects with prior Grade 1 infusion reaction may be pre-medicated as per Grade 2 infusion reactions.

[c] Subjects with prior Grade 2 infusion reaction may be pre-medicated as per Grade 3 infusion reactions.

If a subject with a prior Grade 2 to 3 infusion reaction also requires dose reduction of dexamethasone, the dexamethasone dose on the days of elotuzumab infusion should be no less than 8 mg IV (on the day of elotuzumab infusion at least 45 minutes before elotuzumab).

Subjects with Grade 4 infusion reaction are not eligible to receive additional elotuzumab. These subjects may continue to receive pomalidomide and dexamethasone.

4.5.3.3 Elotuzumab Infusion Rate

During the first cycle, the elotuzumab infusion rate will be increased gradually to a maximum of 5 mL/min as presented in the table below. An infusion rate increase to the next higher level is permitted only if no infusion reactions are encountered.

Table 4.5.3.3-1: Elotuzumab Infusion Rate

Infusion Rate	Duration of infusion	Volume delivered	Volume remaining
Cycle 1 Dose 1	Approximate Total Duration: 2hrs 50min		262 mL*
0.5 mL/min	30 min	15 mL	247 mL
1 mL/min	30 min	30 mL	217 mL
2 mL/min	110 min	217 mL	0 mL
Cycle 1 Dose 2	Approximate Total Duration: 1hr 13min		262 mL
3 mL/min	30 min	90 mL	172 mL
4 mL/min	43 min	172 mL	0 mL
Cycle 1 Dose 3 and 4	Approximate Total Duration: 53min		262 mL
5 mL/min	53 min	262 mL	0 mL
Cycle 2 +	Approximate Total Duration: 53min		262 mL
5 mL/min	53 min	262 mL	0 mL

* Volume for 80 kg subject. Total volume varies according to the subject weight.

Please note that infusion rate increase to the next higher level only if no infusion reactions encountered.

4.5.4 Nivolumab

Nivolumab will be administered at a dose of 240 mg as an intravenous infusion over 30 minutes every 2 weeks (Days 1 and 15 of each 28 day cycle) during Cycles 1 through 4. Starting Cycle 5 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).

Nivolumab should be administered before elotuzumab.

When administering Q2W, subjects may be dosed no less than 12 days from the previous dose. There are no premedications recommended for nivolumab on the first cycle.

Nivolumab can be delayed within a 3 day window of Day 1 and Day 15, during cycles 1 through 4, as long as the 12 day interval between 2 nivolumab doses is respected.

When administering Q4W, subjects may be dosed no less than 21 days from the previous dose. During cycles 5 and beyond, nivolumab can be delayed within a week.

Doses that fall outside the allowed window, regardless of the schedule, should be skipped.

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 4.5.6.

There will be no dose escalations or reductions of nivolumab allowed. Doses of nivolumab may be interrupted, delayed, or discontinued in accordance with Section 4.5.8 depending on how well the subject tolerates the treatment.

4.5.5 Guidelines for Elotuzumab Infusion in Subjects with Infusion Reactions

4.5.5.1 Grade 1 Infusion Reaction

Grade 1 elotuzumab infusion-related reactions by definition do not require intervention; however, increased monitoring is recommended.

4.5.5.2 Grade 2 or 3 Infusion Reaction

Infusion reactions during the elotuzumab infusion: For a Grade 2 or 3 elotuzumab infusion-related reaction, the infusion must be interrupted. The subject should be treated as clinically indicated with one or more of the following medications or interventions: antiemetics, antihistamines, analgesics, corticosteroids, leukotriene inhibitors, oxygen inhalation, epinephrine, bronchodilators, or other supportive measures as indicated.

Once the elotuzumab infusion-related reaction has resolved to Grade ≤ 1, the infusion can be restarted at 0.5 mL/minute. If symptoms do not recur after 30 minutes, the infusion rate may be increased in a stepwise fashion (0.5 mL/minute every 30 minutes) to the rate at which the infusion reaction occurred. If no recurrence of the infusion reaction, the escalation regimen can be resumed. Subjects who experience an infusion reaction require vital signs to be monitored every 30 minutes for 1 or 2 hours after the end of the elotuzumab infusion (as clinically indicated). If the elotuzumab infusion reaction recurs, the infusion must be stopped and not restarted on that day. Appropriate therapy should be administered to address the subject's signs and symptoms. The infusion can be reattempted at the next protocol defined infusion time point at the investigator's discretion with additional premedication as described throughout Section 4.5.3.1

Infusion reactions after the completion of elotuzumab infusion: Should a Grade 2 or 3 infusion reaction occur following completion of an elotuzumab infusion, the subject should be treated as clinically indicated with 1 or more of the following medications or interventions: diphenhydramine, acetaminophen, hydrocortisone, H2 inhibitor, leukotriene inhibitor, oxygen inhalation, epinephrine, bronchodilators, or other supportive measures as indicated.

Elotuzumab infusions on subsequent weeks after a prior Grade 2 or 3 infusion reaction: Subjects with prior Grade 2 or 3 infusion reactions should have the next infusion started at 0.5 mL/min and then escalated in a stepwise fashion (0.5 mL/minute every 30 minutes) to the rate at which the infusion reaction occurred. If no Grade ≥ 2 infusion reaction occurs, the escalation regimen may be resumed and the next infusion may be initiated as planned per the regimen.

4.5.5.3 Grade 4 Infusion Reaction

Subjects with a Grade 4 elotuzumab infusion reaction must have elotuzumab permanently discontinued.

4.5.6 Treatment of Nivolumab-Related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is 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, arthralgia, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or

4 infusion reactions should be reported within 24 hours to the study medical monitor and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (Version 3.0) 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):

- 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 required 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 ensue 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 SoluCortef or equivalent) may be used.

For **Grade 3 or 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 ventilator 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 of the symptoms.

In 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).

4.5.7 Management Algorithms for Immune Related Adverse Events

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab is considered an immuno-oncology agent in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Management Algorithms have been developed to assist investigators in assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathy
- Skin
- Neurological

The above algorithms are found in Appendix 7 and in the nivolumab Investigator Brochure.

4.5.8 Dose Delay, Interruption, or Discontinuation for All Subjects

Please refer to Sections 4.5.8.1, 4.5.8.2, 4.5.8.3, and 4.5.8.4 for drug-specific delay guidance.

For each cohort, if the dose of one drug in the regimen (ie, pomalidomide, dexamethasone, nivolumab, or elotuzumab) is delayed, interrupted, or discontinued, the treatment with the other drugs may continue as scheduled. However, in the EPd cohort, if dexamethasone is delayed or discontinued discuss ongoing elotuzumab administration with the Medical Monitor. Subjects experiencing a 56 day delay in all study drugs due to an adverse event(s) related to study treatment must be discontinued from study drug. Subjects experiencing delays unrelated to study therapy, for example due to radiation therapy, may delay study treatment after discussion with the medical monitor.

Each cycle is 28 days. While dose delays 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. Missed doses should be skipped, not delayed, if not given within the allowed window.

Subjects may continue on study therapy even if components of the study therapy must be discontinued. For example, a subject may continue on study therapy if elotuzumab must be discontinued for an adverse event or other reason. Patients are considered still on study therapy even if they continue solely on pomalidomide, dexamethasone, or nivolumab.

4.5.8.1 Dose Delay for Elotuzumab

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

Beginning with Cycle 3 and beyond, elotuzumab 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 elotuzumab continues per the protocol defined schedule.

Subjects experiencing a Grade 4 infusion reaction related to elotuzumab must permanently discontinue elotuzumab.

4.5.8.2 Dose Delay for Dexamethasone

Dexamethasone interruption should be performed as clinically indicated at the discretion of the investigator.

The weekly dexamethasone that coincides with or is temporally closest to the next elotuzumab dosing must be administered as part of the premedication for elotuzumab per the guidance in Section 4.5.3.1.

4.5.8.3 Dose Delay for 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

4.5.8.4 Dose Delay for Nivolumab

Nivolumab administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related adverse event, with the following exceptions:
  - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay/ interruption.
- Any Grade 3 skin, drug-related adverse event
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, AST, ALT, or total bilirubin or asymptomatic amylase or lipase:
  - Grade 3 lymphopenia does not require dose delay/interruption
  - If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay/interrupt dosing for drug-related Grade ≥ 2 toxicity.
  - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay/interrupt dosing for drug-related Grade ≥ 3 toxicity.
  - Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay/interruption.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Subjects who require delay/interruption of nivolumab should be re-evaluated as clinically indicated and resume nivolumab dosing, as per the protocol dosing schedule when re-treatment criteria are met.

4.5.8.5 Criteria to Resume Treatment with Nivolumab

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 (Section 4.5.8.6) 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 in Section 4.5.8.6. There will be no dose reductions for nivolumab.

4.5.8.6 Nivolumab Dose Discontinuation

Nivolumab treatment should be permanently discontinued for the following:

- 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 adverse event 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, 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
  - 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

- ♦ Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
  - AST or ALT > 5-10 x ULN for 2 weeks
  - AST or ALT > 10 x ULN
  - Total bilirubin > 5 x ULN
  - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
  - Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
- – Grade 4 neutropenia ≤ 7 days
- – Grade 4 lymphopenia or leukopenia
- – Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis. The BMS Medical Monitor should be consulted for Grade 4 amylase or lipase abnormalities.
- – 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 adrenal insufficiency, ACTH deficiency, 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 adverse events 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 adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.

4.5.9 Recommended Dose Reduction

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. 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.

4.5.9.1 Elotuzumab and Nivolumab

No dose reduction is allowed for elotuzumab or nivolumab.

4.5.9.2 Dexamethasone

Dexamethasone dose reductions for toxicity related to study drug, must be performed as clinically indicated. Recommended management is described in Table 4.5.9.2-1 and Table 4.5.9.2-2. Deviations to the recommended dose reductions are allowed based on the clinical judgment of the investigator.

Table 4.5.9.2-1: Dexamethasone Dose Reductions

CTCAE Category	Adverse Event	Treatment Adjustment
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, gastritis	Treat with a proton pump inhibitor.
	Grade 1 - 2 (requiring medical management)	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.

Contact the medical monitor to discuss dexamethasone premedication for subjects who reach dose level -3 or must discontinue dexamethasone due to toxicity.

Table 4.5.9.2-2: Dexamethasone Dose Levels

Dose Level	Reducing Dexamethasone on Weeks with Elotuzumab		Reducing Dexamethasone on Weeks Without Elotuzumab	
	PO	IV	PO	IV
0	≤ 75 years old - 28 mg > 75 years old - 8 mg	8 mg	≤ 75 years old - 40 mg > 75 years old - 20 mg	N/A
-1	≤ 75 years old - 12 mg > 75 years old - 8 mg	8 mg	≤ 75 years old - 20 mg > 75 years old - 12 mg	N/A
-2	≤ 75 years old - 0 mg > 75 years old - 0 mg	8 mg	≤ 75 years old - 12 mg > 75 years old - 8 mg	N/A
-3	≤ 75 years old - 0 mg > 75 years old - 0 mg	Contact Medical Monitor	≤ 75 years old - 0 mg > 75 years old - 0 mg	N/A

4.5.9.3 Pomalidomide

Below are the recommended dose adjustments for the management of NCI CTCAE Grade 3 and 4 toxicities for thrombocytopenia and neutropenia judged by the investigator to be related to pomalidomide. Information in Table 4.5.9.3-1 and Table 4.5.9.3-2 is based on pomalidomide prescribing information, which contains additional guidance on pomalidomide dosing.[29,31]

Table 4.5.9.3-1: 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 4.5.9.3-2: 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 ≥ 500 per mm^3	Resume pomalidomide at 3 mg daily

Table 4.5.9.3-2: Treating Neutropenia Related to Pomalidomide

When Neutrophil Count:	Recommended Course:
For each subsequent drop < 500 mm^3	Interrupt pomalidomide treatment
Return to ≥ 500 mm^3	Resume pomalidomide at 1 mg less than previous dose

ANC, absolute neutrophil count.

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%.[29,31]

4.5.10 EN Cohort: Stopping Rules for Unacceptable Toxicity

The rate of AE occurrence will be assessed on an ongoing basis during treatment and within 100 days of last dose of therapy with nivolumab.

Enrollment in the EN cohort and continued treatment of patients already enrolled in the EN cohort will be stopped if either of the safety signals below are observed:

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

4.6 Blinding/Unblinding

Not applicable.

4.7 Treatment Compliance

Starting at Cycle 1, Day 1, all treated subjects will be assessed for drug compliance of all treatments administered during the course of the study. Treatment compliance will be monitored by drug accountability and recorded in the subject's medical record. For those medications taken at home (PO dexamethasone and pomalidomide), subjects will be provided with a medication diary in which to record study drug doses and will be instructed to bring this diary and study drug containers to clinic visits.

4.8 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 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 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.

4.9 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 Study Monitor.

5. STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Procedural Outline (CA204142)

Procedure	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	Prior to any screening procedures
Inclusion/Exclusion Criteria	X	Within 14 days prior to first dose of study drug
Medical History/Treatment History	X	
Safety Assessments		
Physical Examination	X	Includes height and weight within 14 days prior to first dose of study drug
Vital Signs	X	Temperature, BP, HR, within 14 days prior to first dose of study drug
Performance Status (ECOG)	X	Within 14 days prior to first dose of study drug
Serious Adverse Events Assessment	X	Collected from the time of informed consent
Concomitant Medications	X	Within 14 days prior to first dose of study drug
ECG	X	Within 28 days of randomization
Laboratory Assessments		
CBC, differential, platelets	X	Within 14 days prior to first dose of study drug
Chemistry	X	Within 14 days prior to first dose of study drug (See Section 5.3.4)
Serum β2-microglobulin	X	Within 28 days prior to first dose of study drug (Central Lab Analysis)
Albumin	X	Within 28 days prior to first dose of study drug
Pregnancy Test	X	For WOCBP only, 2 pregnancy tests, one 10 - 14 days prior to start of study drug and one within 24 hours prior to start of study drug. Urine tests must have a sensitivity of at least 25 IU/L.
Thyroid Function Tests (TFTs) (reflex to free T3/total T3, free T4 for abnormal TSH result).	X	Within 28 days prior to first dose of study drug. Required only after Amendment 02.

Table 5.1-1: Screening Procedural Outline (CA204142)		
Procedure	**Screening Visit**	**Notes**
Hepatitis B surface antigen (HBsAg), and hepatitis C antibody (HCV Ab) or HCV ribonucleic acid (RNA).	X	Within 28 days prior to first dose of study drug. Required only after Amendment 02.
[redacted]		

Table 5.1-2: CA204142 Cycles 1 and 2 - EPd Cohort Only

Procedure	Day 1	Day 8	Day 15	Day 22	Rest Days 23 – 28	Notes
Safety Assessments						
Targeted Physical Examination	X					Perform prior to dosing, include weight
Vital Signs	X	X	X	X		Cycle 1: Measure vital signs pre-elotuzumab infusion, 30 minutes after the start of elotuzumab infusion, at the end of infusion, and 30 minutes after the completion of infusion Cycle 2 and beyond: evaluate prior to dosing
Performance Status (ECOG)	X					Evaluate prior to dosing
Serious Adverse Event Assessment	X	X	X	X		Evaluate prior to dosing
Adverse Events Assessment	X	X	X	X		Evaluate prior to dosing
Concomitant Medications	X	X	X	X		Evaluate prior to dosing
Laboratory Tests						
CBC, differential, platelets	X	X	X	X		Can be drawn up to 3 days prior to study visit (See Section 5.3.4). Screening results are sufficient for Cycle 1
Chemistry	X					Can be drawn up to 3 days prior to study visit
Pregnancy Test	X					For WOCBP only. Urine tests must have a sensitivity of at least 25 IU/L. Test within 24 hours of Dose 1 study medication.
Efficacy Assessments						
Myeloma Urine and Serum Lab tests	(Central Lab Analysis) Every 4 weeks from date of first dose of study drug until disease progression					Day 1 of each cycle (except Cycle 1 - refer to Screening visit for defined window as listed on Table 5.1-1) (See also: Section 5.4.2) 24-hour urine sample can be collected within ± 7 days of visit, and must be obtained in all subjects who have measurable UPEP M protein (≥ 200 mg/24 hours) at baseline with each cycle. See Section 5.4.2 for subjects without measurable urine M protein at baseline and no FLC detected by the serum test.

Table 5.1-2: CA204142 Cycles 1 and 2 - EPd Cohort Only

Procedure	Day 1	Day 8	Day 15	Day 22	Rest Days 23 – 28	Notes
Bone Marrow Aspiration/Biopsy	For confirmation of CR if applicable or, if clinically indicated at time of suspected disease progression					Bone marrow aspirate is mandatory. Bone marrow biopsy is optional. Bone marrow will be analyzed in local laboratory, with performance of IHC and/or flow cytometry to assess for sCR.
Skeletal Imaging	If clinically indicated					
CT/MRI assessment	As clinically indicated					
Response per IMWG uniform criteria	Every 4 weeks from date of first dose of study drug on Cycle 1 Day 1 until progression. (Cycles cannot be delayed. In the event that the first dose within a cycle is delayed or omitted, the tumor assessment should still be done on Day 1 of the cycle and should not be delayed until dosing.).					Subjects who discontinue from study treatment for reasons other than progression will continue to have tumor assessment every 4 weeks from C1D1 until progression.

Table 5.1-3: CA204142 Cycles 3 and Beyond - EPd Cohort and Cross-over Patients from EN Cohort

Procedure	Day 1	Day 8	Day 15	Day 22	Rest Days 23 - 28	End of Treatment	Days 30 & 60 post end of treatment*	Notes
Safety Assessments								
Targeted Physical Examination	X							Perform prior to dosing, includes weight
Vital Signs	X					X		Evaluate prior to dosing.
Performance Status (ECOG)	X					X		Evaluate prior to dosing
Serious Adverse Event Assessment	X					X	X	Evaluate prior to dosing SAEs will be collected for EPd subjects up to 100 days of last dose (per Section 6.1.1).
Adverse Events Assessment	X					X	X	Evaluate prior to dosing
Concomitant Medications	X					X	X	Evaluate prior to dosing
Laboratory Tests								
CBC, differential, platelets	X					X		Can be drawn up to 3 days prior to visit. Additional samples as clinically indicated.
Chemistry	X					X		Can be drawn up to 3 days prior to visit (See Section 5.3.4)
Pregnancy Test	X					X	X	For WOCBP only. Tests must occur within 24 hours prior to dosing. The pregnancy test should occur on Days 1 of each cycle. Urine tests must have a sensitivity of at least 25 IU/L. Pregnancy test must also be performed at end of treatment and at 30, 60 and 90 days off treatment. The test at 90 days off treatment may be performed locally if the patient is not scheduled to return to the center for other reasons.

Table 5.1-3: CA204142 Cycles 3 and Beyond - EPd Cohort and Cross-over Patients from EN Cohort

Procedure	Day 1	Day 8	Day 15	Day 22	Rest Days 23 - 28	End of Treatment	Days 30 & 60 post end of treatment*	Notes
Efficacy Assessments								
Myeloma Urine and Serum Lab tests	(Central Lab Analysis) Every 4 weeks from date of first dose of study drug until disease progression							Day 1 of each cycle (except Cycle 1 - refer to Screening visit for defined window). 24-hour urine sample can be collected within ± 7 days of visit and must be obtained in all subjects who have measurable UPEP M protein (≥ 200 mg/24 hours) at baseline with each cycle. See Section 5.4.2 for subjects without measurable urine M protein at baseline and no FLC detected by the serum test.
Bone Marrow Aspiration/Biopsy	For confirmation of CR if applicable or, if clinically indicated at time of suspected disease progression							Bone marrow aspirate is mandatory. Bone marrow biopsy is optional. Bone marrow will be analyzed in local laboratory, with performance of IHC and/or flow cytometry to assess for sCR.
Corrected calcium	Every 4 weeks from the date of the first dose of study drug until disease progression, regardless of whether the subject is on study therapy or subsequent therapy.							Serum calcium and albumin from peripheral blood at D1 of each cycle until disease progression, even if subject is on subsequent therapy; if used as criterion for disease progression, must be confirmed by second value.
Skeletal Imaging	If clinically indicated							
CT/MRI assessment	As clinically indicated							

Table 5.1-3: CA204142 Cycles 3 and Beyond - EPd Cohort and Cross-over Patients from EN Cohort

Procedure	Day 1	Day 8	Day 15	Day 22	Rest Days 23 - 28	End of Treatment	Days 30 & 60 post end of treatment*	Notes
Response per IMWG uniform criteria	Every 4 weeks from date of first dose of study drug on Cycle 1 Day 1 until progression. (Cycles cannot be delayed. In the event that the first dose within a cycle is delayed or omitted, the tumor assessment should still be done on Day 1 of the cycle and should not be delayed until dosing.).							Subjects who discontinue from study treatment for reasons other than progression will continue to have tumor assessment every 4 weeks from C1D1 until progression. Following disease progression, subjects will be followed at least annually for survival.

* Subjects in the EN cohort who cross-over to the EPd cohort but discontinue treatment within 2 cycles of EPd treatment will still need to undergo 100 day follow-up visit from last dose of nivolumab to evaluate safety events related to study treatment.

Table 5.1-4: CA204142 Cycles 1 and 2 - EN Cohort

Procedure	Day 1	Day 8	Day 15	Day 22	Rest Days 23 – 28	Notes
Safety Assessments						
Targeted Physical Examination	X					Perform prior to dosing, include weight
Vital Signs	X	X	X	X		Cycle 1: Measure vital signs pre-elotuzumab infusion, 30 minutes after the start of elotuzumab infusion, at the end of infusion, and 30 minutes after the completion of infusion Cycle 2 and beyond: Evaluate prior to dosing. Vital signs must be collected if infusion related AE occurs.
Performance Status (ECOG)	X					Evaluate prior to dosing
Serious Adverse Event Assessment	X	X	X	X		Evaluate prior to dosing
Adverse Events Assessment	X	X	X	X		Evaluate prior to dosing
Concomitant Medications	X	X	X	X		Evaluate prior to dosing
Second Primary Malignancy	X					
Laboratory Tests						
CBC, differential, platelets	X	X	X	X		Can be drawn up to 3 days prior to study visit (See Section 5.3.4). Screening results are sufficient for Cycle 1
Chemistry	X					Can be drawn up to 3 days prior to study visit
Pregnancy Test	X					For WOCBP only. Urine tests must have a sensitivity of at least 25 IU/L. Test within 24 hours of Dose 1 study medication.

Table 5.1-4: CA204142 Cycles 1 and 2 - EN Cohort

Procedure	Day 1	Day 8	Day 15	Day 22	Rest Days 23 – 28	Notes
Thyroid stimulating hormone (TSH) (reflex to free T3/total T3, free T4 for abnormal TSH result).	X*					To be performed every *2 cycles (± 7 days) from first dose regardless of dosing schedule
Efficacy Assessments						
Myeloma Urine and Serum Lab tests (SPEP/EPEP/sFLC/ Igs)	(Central Lab Analysis) Every 4 weeks from date of first dose of study drug until disease progression of study drug until disease progression regardless of whether subject is on study therapy or subsequent therapy					Day 1 of each cycle (Optional at C1D1 if conducted at screening.) (See also: Section 5.4.2) 24-hour urine sample can be collected within ± 7 days of visit, and must be obtained in all subjects
Bone Marrow Aspiration/Biopsy	For confirmation of CR, if applicable or, if clinically indicated at time of suspected disease progression (Local Lab analysis)					Bone Marrow plasma cell percentage. Performance of IHC or flow cytometry to assess for sCR (for subjects with CR).
Corrected Calcium	Every 4 weeks from the date of the first dose of study drug until disease progression, regardless of whether the subject is on study therapy or subsequent therapy.					Serum calcium and albumin from peripheral blood at D1 of each cycle until disease progression, even if subject is on subsequent therapy; if used as criterion for disease progression, must be confirmed by second value.
Skeletal Imaging	If clinically indicated					
CT/MRI assessment	As clinically indicated and at the time of CR/sCR assessments					
Response per IMWG uniform criteria	Every 4 weeks from date of first dose of study drug on Cycle 1 Day 1 until progression. (Cycles cannot be delayed. In the event that the first dose within a cycle is delayed or omitted, the tumor assessment should still be done on Day 1 of the cycle and should not be delayed until dosing.).					Subjects who discontinue from study treatment for reasons other than progression will continue to have tumor assessment every 4 weeks from C1D1 until progression. Response assessments and PD require confirmation (2 consecutive assessments made at any time) before the institution of any new therapy.

Table 5.1-4: CA204142 Cycles 1 and 2 - EN Cohort

Procedure	Day 1	Day 8	Day 15	Day 22	Rest Days 23 – 28	Notes
[redacted]						

Table 5.1-5: CA204142 Cycles 3 and 4 - EN Cohort

Procedure	Day 1	Day 8	Day 15	Day 22	Rest Days 23 – 28	Notes
Safety Assessments						
Targeted Physical Examination	X					Perform prior to dosing, include weight
Vital Signs	X		X			Evaluate prior to dosing.
Performance Status (ECOG)	X					Evaluate prior to dosing
Serious Adverse Event Assessment	X		X			Evaluate prior to dosing
Adverse Events Assessment	X		X			Evaluate prior to dosing
Concomitant Medications	X		X			Evaluate prior to dosing
Second Primary Malignancy	X					
Laboratory Tests						
CBC, differential, platelets	X					Can be drawn up to 3 days prior to study visit (See Section 5.3.4).
Chemistry	X					Can be drawn up to 3 days prior to study visit
Pregnancy Test	X					For WOCBP only. Urine tests must have a sensitivity of at least 25 IU/L. Test within 24 hours.

Table 5.1-5: CA204142 Cycles 3 and 4 - EN Cohort

Procedure	Day 1	Day 8	Day 15	Day 22	Rest Days 23 – 28	Notes
Thyroid stimulating hormone (TSH) (reflex to free T3/total T3, free T4 for abnormal TSH result).	X*					To be performed every *2 cycles (± 7 days) from first dose regardless of dosing schedule.
Efficacy Assessments						
Myeloma Urine and Serum Lab tests (SPEP/UPEP/sFLC/Igs)	(Central Lab Analysis) Every 4 weeks from date of first dose of study drug until disease progression regardless of whether subject is on study therapy or subsequent therapy					Day 1 of each cycle (See also: Section 5.4.2) 24-hour urine sample can be collected within ± 7 days of visit, and must be obtained in all subjects
Bone marrow aspiration/biopsy	For confirmation of CR, if applicable, or if clinically at the time of suspected disease progression (local lab analysis)					Bone marrow plasma cell percentage Performance of IHC or flow cytometry to assess for sCR (for subjects with CR).
Corrected Calcium	Every 4 weeks from the date of the first dose of study drug until disease progression, regardless of whether the subject is on study therapy or subsequent therapy.					Serum calcium and albumin from peripheral blood at D1 of each cycle until disease progression, even if subject is on subsequent therapy; if used as criterion for disease progression, must be confirmed by second value.
Skeletal Imaging	If clinically indicated					
CT/MRI assessment	As clinically indicated and at the time of CR/sCR assessments					
Response per IMWG uniform criteria	Every 4 weeks from date of first dose of study drug on Cycle 1 Day 1 until progression. (Cycles cannot be delayed. In the event that the first dose within a cycle is delayed or omitted, the tumor assessment should still be done on Day 1 of the cycle and should not be delayed until dosing.).					Subjects who discontinue from study treatment for reasons other than progression will continue to have tumor assessment every 4 weeks from C1D1 until progression. Response assessments and PD require confirmation (2 consecutive assessments made at any time) before the institution of any new therapy.

Table 5.1-5: CA204142 Cycles 3 and 4 - EN Cohort

Procedure	Day 1	Day 8	Day 15	Day 22	Rest Days 23 – 28	Notes
[redacted]						

Table 5.1-6: CA204142 Cycles 5 and Beyond - EN Cohort

Procedure	Day 1	Day 8	Day 15	Day 22	Rest Days 23 - 28	End of Treatment	Days 30 & 100 (+/- 7 days) post end of treatment	Notes
Safety Assessments								
Targeted Physical Examination	X							Perform prior to dosing, includes weight
Vital Signs	X					X		Evaluate prior to dosing.
Performance Status (ECOG)	X					X		Evaluate prior to dosing
Serious Adverse Event Assessment	X					X	X	Evaluate prior to dosing
Adverse Events Assessment	X					X	X	Evaluate prior to dosing
Concomitant Medications	X					X	X	Evaluate prior to dosing
Second Primary Malignancy	X					X	X	
Laboratory Tests								
CBC, differential, platelets	X					X		Can be drawn up to 3 days prior to visit. Additional samples as clinically indicated.
Chemistry	X					X		Can be drawn up to 3 days prior to visit (See Section 5.3.4)

Table 5.1-6: CA204142 Cycles 5 and Beyond - EN Cohort

Procedure	Day 1	Day 8	Day 15	Day 22	Rest Days 23 - 28	End of Treatment	Days 30 & 100 (+/- 7 days) post end of treatment	Notes
Pregnancy Test	X					X	X	For WOCBP only. Tests must occur within 24 hours prior to dosing. The pregnancy test should occur on Days 1 of each cycle. Urine tests must have a sensitivity of at least 25 IU/L. **Pregnancy test must also be performed at end of treatment and at 30, 60 and 90 days off treatment**. The test at 90 days off treatment may be performed locally if the patient is not scheduled to return to the center for other reasons.
Thyroid stimulating hormone (TSH) (reflex to free T3/total T3, free T4 for abnormal TSH result).	X					X		To be performed every 2 cycles (± 7 days) from first dose regardless of dosing schedule.
Efficacy Assessments								
Myeloma Urine and Serum Lab tests (SPEP/UPEP/sFLC/Igs)	(Central Lab Analysis) Every 4 weeks from date of first dose of study drug until disease progression regardless of whether subject is on study therapy or subsequent therapy							Day 1 of each cycle (including Cycle 1 See also Section 5.4.2) 24-hour urine sample can be collected within ± 7 days of visit, and must be obtained in all subjects
Bone marrow aspiration/biopsy	For confirmation of CR, if applicable or if clinically indicated at the time of suspected disease progression (local lab analysis).							Bone marrow plasma cell percentage Performance of IHC or flow cytometry to assess for a sCR (for subjects with CR).
Skeletal Imaging	If clinically indicated							
CT/MRI assessment	As clinically indicated							

Table 5.1-6: CA204142 Cycles 5 and Beyond - EN Cohort

Procedure	Day 1	Day 8	Day 15	Day 22	Rest Days 23 - 28	End of Treatment	Days 30 & 100 (+/- 7 days) post end of treatment	Notes
Response per IMWG uniform criteria	Every 4 weeks from date of first dose of study drug on Cycle 1 Day 1 until progression. (Cycles cannot be delayed. In the event that the first dose within a cycle is delayed or omitted, the tumor assessment should still be done on Day 1 of the cycle and should not be delayed until dosing.). Response assessments (≥ PR) and PD require confirmation (2 consecutive assessments made at any time before the institution of new therapy).							Subjects who discontinue from study treatment for reasons other than progression will continue to have tumor assessment every 4 weeks from C1D1 until progression. Following disease progression, subjects will be followed at least annually for survival.
[redacted]								

5.1.1 Retesting During Screening Period

Retesting of laboratory parameters and/or other assessments within any single Screening period will be permitted (in addition to any parameters that require a confirmatory value).

Any new result will override the previous result (ie, the most current result prior to Treatment) and is the value by which study inclusion will be assessed, as it represents the subject's most current, clinical state.

Laboratory parameters and/or assessments that are included in Screening Procedural Outline may be repeated in an effort to find all possible well-qualified subjects. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

5.2 Study Materials

The following will be distributed to sites for use in this study:

- Instructions and kits for collections, processing, and shipment of blood and tissue samples
- NCI CTCAE booklets version 3.0
- Elotuzumab Investigator Brochure
- Nivolumab Investigator Brochure
- Pomalidomide (Pomalyst®) Package Insert
- Site Manual for operation of IVRS
- Subject Dosing Diary
- Serious Adverse Event (SAE) Case Report Form (CRF/eCRF) pages
- Pregnancy Surveillance Forms

5.3 Safety Assessments

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 submitted to BMS at least once per cycle. In addition, all safety lab results that lead to dose delay or discontinuation must be submitted to BMS.

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 Imaging Assessment for the Study

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the Study Investigator as per standard medical/clinical judgment.

5.3.2 Vital Signs, Physical Measurements, and Physical Examination

Vital signs (body temperature, blood pressure and heart rate) will be recorded as outlined in Table 5.1-1, Table 5.1-2, Table 5.1-3, Table 5.1-4 , Table 5.1-5, and Table 5.1-6. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes prior to dosing. On Cycle 1 only, the days of elotuzumab dosing, vital signs monitoring should be performed as follows:

- Prior to the start of the elotuzumab infusion
- Thirty minutes after the start of infusion
- At the end of the infusion
- Thirty minutes post completion of the elotuzumab infusion.
- Subjects who experience a Grade ≥ 2 infusion reaction require vital signs to be monitored every 30 minutes for 1- 2 hours (as clinically indicated) after the end of the elotuzumab infusion.

Height will be recorded at screening. Weight will be measured at study visits as indicated in Table 5.1-1, Table 5.1-2, Table 5.1-3, Table 5.1-4, Table 5.1-5, and Table 5.1-6.

A full physical examination will be performed at the screening visit, whereas a targeted exam will occur at Day 1 and during on-treatment up to 3 days prior to dosing and post-treatment visits. A targeted physical examination may be performed by a qualified professional guided by the examiner's observations and/or subject complaints on new or changed conditions, symptoms, or concerns. Targeted physical exam includes assessment of heart, lung, and abdomen.

5.3.3 Performance Status

Performance assessment will be performed as indicated in Table 5.1-1, Table 5.1-2, Table 5.1-3, Table 5.1-4, Table 5.1-5, and Table 5.1-6 using ECOG performance scale and criteria as described in Appendix 2.

5.3.4 Laboratory Assessments for Safety

Laboratory assessments for safety will be performed at local laboratories. Safety laboratory assessments are listed in Table 5.3.4-1.

Table 5.3.4-1: Safety Laboratory Assessments

Safety Laboratory Assessments	Screening as outlined in Table 5.1-1. Within 14 days of first dose of study drug	Study Visits as outlined in Table 5.1-2,Table 5.1-3, Table 5.1-4, Table 5.1-5, and Table 5.1-6.
Hematology		
CBC	X	X
Differential	X	X
Platelets	X	X
Chemistry		
Sodium	X	X
Potassium	X	X
Chloride	X	X
Albumin	X (within 28 days of first dose of study drug)	X
Alkaline Phosphatase	X	X
ALT (SGPT)	X	X
AST (SGOT)	X	X
Total Bilirubin	X	X
Lactate Dehydrogenase	X	X
BUN (or Urea)	X	X
Creatinine	X	X
Glucose	X	X
Calcium	X	X
Pregnancy Test		
Urine or Serum Pregnancy	X (2 tests: one 10 - 14 days prior to the start of study drug and one within 24 hours prior to the start of study drug)	X Pregnancy test must also be performed at end of treatment, and at 30, 60 and 90 days off treatment. The test at 90 days off treatment may be performed locally if the patient is not scheduled to return to the center for other reasons. Urine tests must have a sensitivity of at least 25 IU/L.
Hepatitis B surface antigen (HBV sAg, Australia antigen) and hepatitis C antibody (HCV Ab) or HCV ribonucleic acid (RNA)	X[a]	

Table 5.3.4-1: Safety Laboratory Assessments

Safety Laboratory Assessments	Screening as outlined in Table 5.1-1. Within 14 days of first dose of study drug	Study Visits as outlined in Table 5.1-2,Table 5.1-3, Table 5.1-4, Table 5.1-5, and Table 5.1-6.
Thyroid stimulating hormone (TSH) (reflex to free T3, free T4 or abnormal result)	X[a]	X[b]

[a] Within 28 days of first dose of study drug

[b] TSH (reflex to free/total T3, free T4 for abnormal result) to be performed every 2 cycles (± 7 days) from first dose regardless of schedule.

5.4 Efficacy Assessments

Efficacy endpoints will be based on analysis of serum and urine electrophoresis (SPEP and UPEP), sFLC (for those with sFLC disease only), corrected calcium (serum calcium and serum albumin), imaging and bone marrow assessments, all at predefined intervals as specified in Table 5.1-1, Table 5.1-2, Table 5.1-3, Table 5.1-4, Table 5.1-5, and Table 5.1-6. Assessments done at local labs versus central labs are indicated in Table 5.1-1, Table 5.1-2, Table 5.1-3, Table 5.1-4, Table 5.1-5, and Table 5.1-6. Assessments for SPEP and UPEP and molecular MRD will be based on central lab results, whereas assessments of bone marrow, bone lesions, extramedullary plasmacytomas, and corrected calcium will be based on local analysis at the site.

5.4.1 Primary Efficacy Assessment

Response criteria according to guidelines of the modified IMWG[33,34] (Appendix 4) will be used for the primary analysis. For the purposes of this study, all subjects' tumor assessments by myeloma laboratory tests should be re-evaluated per the protocol-stated frequency relative to the date of first dose of study drug until disease progression based on the modified IMWG criteria, irrespective of dose delays or treatment cycle. **If subject does not have documented disease progression at time of study drug discontinuation, then tumor assessments should still be performed according to the same schedule described above until disease progression.** Subjects will be followed for survival at least once a year by phone after disease progression.

All efficacy laboratory assessments should be done through the central laboratory, except corrected calcium (serum calcium and serum albumin), and bone marrow assessments for plasma cell percentage and light chain restriction (clonality by IHC or flow cytometry). Only if a subject is unable to come to the site for a visit to have specimens collected for a central lab (especially after study drug discontinuation), a SPEP, UPEP, or sFLC assessment can be performed locally, in lieu of a central lab assessment. M protein quantification or Serum Free Light Chain (sFLC) must be performed. Any laboratory samples analyzed locally, including for efficacy, must be entered on the appropriate CRF/eCRF.

5.4.2 Laboratory Assessments for Myeloma

Subjects who have urine M protein of zero mg/24 hours at baseline, but have measurable serum M-protein, do not have to continue UPEP assessments until SPEP M protein values are undetectable. Assessment of UPEP M protein and urine immunofixation at the time of possible CR/sCR is mandatory, that is negative urine immunofixation is required to fulfill CR/sCR criteria, even in subjects with non-measurable values at baseline. Therefore, when serum immunofixation electrophoresis (SIFE) becomes negative, UPEP and urine immunofixation electrophoresis (UIFE) collection should begin for these subjects. In addition, a UPEP should be collected if clinically warranted (for example, signs of disease progression (eg, anemia) even when SPEP M-protein is stable).

1) **Serum**: Serum protein electrophoresis (SPEP) for M protein quantification, immunofixation, and quantitative immunoglobulin assay.
   a) Immunofixation of serum is required at baseline and to confirm CR regardless of whether measurable M-protein was present at baseline.
   b) All other serum tests will be followed at each tumor assessment. Confirmation of ≥ PR is required on 2 consecutive assessments.
2) **Urine**: 24-hour urine collection electrophoresis for M protein quantification and immunofixation.
   a) Immunofixation of urine is required at baseline and to confirm CR regardless of whether measurable M-protein was present at baseline.
   b) All other urine tests will be followed at each tumor assessment Confirmation of ≥ PR is required on 2 consecutive assessments.

[redacted]

5.4.3 Imaging Assessments for Myeloma

5.4.3.1 Skeletal Imaging

Skeletal imaging, by conventional radiography or other methods, for bone lesions will be performed within 60 days prior to first dose of study drug in all EPd cohort subjects and within 28 days in the EN Cohort subjects. Skeletal imaging will be performed on study if clinically indicated. Use of conventional or low dose CT scan (ie, of the spine) or MRI 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.

5.4.3.2 Assessment of Extramedullary Plasmacytoma

Computed tomography or MRI should be performed at screening, if clinically indicated, to assess for extramedullary 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 (ie, 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 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.

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.

5.4.4 Definitions of Response and Progression Criteria

See Appendix 4 for definitions of response and progression. All criteria are derived from IMWG,[33,34] except for minor (minimal) response, which is derived from the European Society for Blood and Marrow Transplantation (EBMT). All response categories require 2 consecutive assessments made before initiation of any new therapy.

5.7 Outcomes Research Assessments

Not applicable

5.8 Other Assessments

5.8.1 Pharmacogenomic/Pharmacogenetic Assessments

Genetic assessment (FISH) of myeloma cells is optional and will be performed by a central laboratory on the fresh bone marrow, during the screening period. If a fresh aspirate is not available, but local genetic assessment has been performed, these results must be entered into the CRF/eCRF. This assessment is considered to be standard of care for myeloma. Aspirates obtained will be used to identify prognostic cytogenetic markers that may include: t(4;14), t(14;16), t(11;14), t(6;14), t(14;20), 1q gains/amp, del(17p), del(1p), and del(13).

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 study drug 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 study drug, whether or not considered related to the study drug.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal 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).

Any component of a study endpoint that is considered related to study therapy (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE (see Section 6.1.1 for reporting details).

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).
- admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events 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. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

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 must 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 must 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 of awareness of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

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

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must 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, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must 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 until 60 days from the last dose of study drug for patients in the EPd cohort and until 100 days from the last dose of study drug for the EN cohort. Subjects in the EN cohort who cross-over to the EPd cohort but discontinue treatment within 2 cycles of EPd treatment will still need to undergo 100 day follow-

up visit from last dose of the nivolumab to evaluate safety events related to study treatment. 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.

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/eCRF (paper or electronic).

Completion of supplemental CRF/eCRFs 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/eCRF 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 study drug, it is subsequently discovered that a female study subject or female partner of male study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during the time to washout (90 days) plus one ovulatory cycle (30 days) for a total of 5 months after product administration (female study subjects); or plus one spermatogenesis cycle (90 days) for a total of 7 months after product administration (female partners of male study subjects), 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 and in accordance with SAE reporting procedures described in Section 6.1.1.

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with BMS, the pregnant subject may continue study drug after a thorough discussion of benefits and risk with the subject.

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

of awareness of the event 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 the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 6.1.1 for reporting details.).

6.6 Potential Drug Induced Liver Injury (DILI)

Specific criteria for identifying potential DILI have not been identified for this protocol. Standard medical practice in identifying and monitoring hepatic issues should be followed.

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.

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).

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

Descriptive statistics (n, mean, median, and standard deviation; minimum, maximum or interquartile range) will be provided for the safety analysis and by subgroups based on types of prior therapy and line of therapy (2L/3L) groups. Because the sample size for the study is small, summary statistics with their associated 95% confidence intervals and tests of hypotheses will be based, to the extent possible, using small-sample statistics like the Clopper-Pearson for binomial data. Median time-to-event and its 95% confidence interval will be based on the Kaplan-Meier (KM) estimation procedure. The KM curves will be presented for time-to-event endpoints.

8.1 Sample Size Determination

8.1.1 EPd Cohort

Seventy-two subjects will be screened with approximately 17% projected to fail screening. This total number is based on logistical consideration with statistical properties outlined below. Screening will continue until a minimum of 60 subjects are enrolled and treated.

Under the assumptions that:

- time to PFS is exponentially distributed
- median time of PFS is 11 months for subjects treated with pomalidomide + dexamethasone and will increase to median of 15 months with the addition of elotuzumab to the treatment mix
- an increase of 4 months in median corresponds to relative risk ratio of 0.73 (0.0462 monthly risk in the elotuzumab add-on and 0.0630 monthly historical risk in the pomalidomide + dexamethasone treated-subjects)

Sixty subjects enrolled over a 24-month period are sufficient to detect an increase in median from 11 to 15 months with about 70% power in a one-sided test with a 0.05 significance level.

Assuming a monthly hazard rate of 0.0462, 48 of the 60 treated subjects are **expected** to have PFS events over a 24-month follow up period.

Power is calculated using PASS12 using the one-sample exponential module where the median is mapped to mean by dividing the assumed alternative median by logarithm of 2. The calculated power and event counts are consistent with power and event counts based on one sample log rank test where the number of events is calculated assuming relative risk ratio of 0.73.

8.1.2 EN Cohort

The planned sample size will be approximately 30 treated subjects; screening will continue until a minimum of 30 patients are enrolled and treated.

For a 30% observed ORR rate and a sample size of N=30 yields an exact confidence interval of [0.15, 0.49]. These design parameters ensure a lower bound higher than 15%.

8.2 Populations for Analyses

- The safety analysis set consists of subjects who receive at least one dose of study drug. The safety analysis set is also the all treated analysis set.
- The efficacy analysis set is the same as the all treated analysis set.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

8.3.1.1 EPd Cohort

PFS is defined as the time from first dosing date to the date of the first documented progression per IMWG uniform criteria or death due to any cause, 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 evaluable assessment. Subjects who did not have any on study efficacy assessments and did not die will be censored on the first dosing date.

Subjects who switched to subsequent therapy prior to documented progression will be censored on the date of the last evaluable assessment prior to the initiation of the new therapy.

8.3.1.2 EN Cohort

ORR is defined as proportion of subjects with best overall response of partial response (PR) or better. Response will be determined per IMWG uniform criteria.

8.3.2 Secondary Endpoint(s)

8.3.2.1 EPd Cohort

- ORR is defined as proportion of subjects with a best overall response of partial response (PR) or better.
- OS is defined as the time from first dosing date to the date of death from any cause. A subject who has not died will be censored at last known date alive.

8.3.2.2 EN Cohort

- PFS definition: See Section 8.3.1.1
- OS is defined as the time from first dosing date to the date of death from any cause. A subject who has not died will be censored at last known date alive.

[redacted]

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

The demographic and baseline characteristics of patients in the safety analysis set will be presented. Among the baseline clinical characteristics are patients' ECOG Performance Status, baseline laboratory assessment for safety and efficacy endpoints, number of prior lines of therapy and types of previous therapy (Appendix 1), and disease status/stage (Appendix 5) at entry.

8.4.2 Efficacy Analyses

The efficacy endpoints, PFS and ORR, will be defined using the IMWG criteria. Responses will be assessed at every treatment cycle using central laboratory test results on myeloma urine and serum, local laboratory bone marrow aspiration test, and if needed bone marrow and skeletal survey results and CT/MRI assessments. Objective responses will include stringent complete

response, complete response, very good partial response and partial responses. The ORR and its 95% confidence interval (CI) using the Clopper-Pearson estimation procedure will be reported. PFS and OS will be plotted using Kaplan-Meier estimates, and if estimable, median and its 95% CI will be reported. Time to response will be analyzed for responders only with summary statistics provided. Duration of response will be reported using K-M estimates. The time to event responses will be recorded from the first day of the first cycle to the day that an event occurs. If no event occurs by the time the study is completed, the patient is censored for that event at the last day of subject contact.

For EPd cohort, the primary analysis of PFS will be conducted when 48 progression events have been observed.

For EN cohort, the primary analyses for ORR will be conducted when enrollment in the EN cohort is complete and all enrolled patients treated with the combination have received at least 3 cycles of treatment.

MRD negativity status for subjects in the EN Cohort will be evaluated by time points. The frequency of the MRD negativity status and the best MRD negativity status will be summarized for the EN cohort. 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 for the EN cohort. Potential association between the first/best MRD negativity status with PFS and OS will be evaluated in all treated patients. Additional details will be presented in the Statistical Analysis Plan.

8.4.3 Safety Analyses

Safety assessments will be performed prior, during and between dosing, and up to 100 days after the last treatment for the EN cohort and 60 days after the last dose in the EPd cohort and for subjects in the EN cohort who cross-over to the EPd cohort but discontinue treatment within 2 cycles of EPd treatment safety assessments will be performed up to 100 days after the last dose of nivolumab. The frequency, severity, relationship to combination of drug treatment, seriousness, and outcomes of adverse events (AEs) will be reported for the full safety analysis set. AE severity will be graded according to the NCI Common Terminology Criteria for Adverse Events 3.0. Results of targeted physical examinations prior to each dosing cycle will be presented.

Summary statistics on vital signs at screening, pre-infusion, 30 minutes after the start of infusion, at end of infusion and 30 minutes after the completion of infusion will be reported for each dosing cycle. Concomitant medications, SAEs, laboratory parameters, and performance status prior to dosing will be presented. The safety analysis set will be used for reporting safety /adverse events.

[redacted]

[redacted]

8.4.6 Outcomes Research Analyses (both cohorts)

Not applicable.

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 done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

BMS representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

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. Certain CRF/eCRF pages and/or electronic files may serve as the source documents.

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRF/eCRFs, 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.

9.1.2.1 Source Documentation

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

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 CRF/eCRFs, 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 study drug (inventoried and dispensed) is maintained at the study site for all investigational products. 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/eCRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to

enhance understanding of product safety. CRF/eCRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the BMS electronic data capture tool, electronic CRF/eCRFs 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/eCRF 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 CRF/eCRFs.

The completed CRF/ECRF, including any paper or electronic SAE/pregnancy CRF/eCRFs, 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 CRF/ECRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRF/eCRFs including records of the changes and corrections.

Each individual electronically signing electronic CRF/eCRFs 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 as appropriate based on the following criteria:

- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)
- 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 must adhere to the publication requirements set forth in the clinical trial agreement (CTA) governing [Study site or Investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to BMS at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

10. GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	If one form of contraception is required, Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. If two forms of contraception is required, Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. **Expanded definition** Complete abstinence as defined as complete avoidance of heterosexual intercourse is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (eg, calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence

11. LIST OF ABBREVIATIONS

Term	Definition
ACTH	adrenocorticotropic Hormone
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
HCG	human chorionic gonadotrophin
BMS	Bristol-Myers Squibb
BMSC	bone marrow stromal cells
BOR	best overall response
BP	blood pressure
BUN	blood urea nitrogen
CBC	complete blood count
CFR	code of Federal Regulations
CI	confidence interval
Cm	centimeter
CR	complete response
CrCLr	creatinine clearance
Cm	centimeter
CRF	case report Form
CSR	clinical study report
dL	deciliter
DOR	duration of response
ECG	electrocardiogram
eCRF	electronic Case Report Form
ECOG	eastern Cooperative Oncology Group
EDC	electronic Data Capture
Eg	exempli gratia (for example)
EMR/EHR	electronic medical/health records
EN	elotuzumab and nivolumab combination cohort
EPd	elotuzumab in combination with pomalidomide and low dose dexamethasone
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
FSH	follicle stimulating hormone
G	gram
GCP	Good Clinical Practice
H	hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus

Term	Definition
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
ICH	International Conference on Harmonisation
Ie	id est (that is)
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IMWG	International Myeloma Working Group
IMP/IP	investigational medicinal products
IND	Investigational New Drug Exemption
I-O	immuno-oncology
IRB	Institutional Review Board
IU	International Unit
IV	intravenous
Kg	kilogram
L	liter
MedDRA	Medical Dictionary for Regulatory Activities
Mg	milligram
Min	minute
mL	milliliter
MR	minimal response
MRD	minimum residual disease
MTD	maximum tolerated dose
µg	microgram
N	number of subjects or observations
N/A	not applicable
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
Ng	nanogram
NIMP	non-investigational medicinal products
ORR	objective response rate
OS	overall survival
PC	plasma cell
PD	pharmacodynamics
PDL-1	programmed death ligand-1
PFS	progression free survival
PK	pharmacokinetics
PR	partial response
PS	performance score
PO	per os (by mouth route of administration)
sCR	stringent complete response
SAE	serious adverse event
SIFE	serum immunofixation electrophoresis

Term	Definition
sFLC	serum free light chain
SIFE	serum immunofixation electrophoresis
SOP	Standard Operating Procedures
SPEP	serum protein electrophoresis
Subj	subject
T	temperature
T	time
TCR	T Cell Receptor
TFTs	thyroid function tests
TSH	thyroid stimulating hormone
TTR	time to response
UIFE	urine immunofixation electrophoresis
UPEP	urine protein electrophoresis
USP	United States Pharmacopoeia
VGPR	very good partial response
WOCBP	women of childbearing potential

APPENDIX 1 DEFINITION OF LINES OF THERAPY

A **line of therapy** is defined by the [redacted] as one or more cycles of a planned treatment program. This may consist of one or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. For example, a planned treatment approach of induction therapy followed by antilogous stem cell transplantation, followed by maintenance is considered one line of therapy. A new line of therapy starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of disease progression, relapse, or toxicity. A new line of therapy also starts when a planned period of observation off therapy is interrupted by a need for additional treatment for the disease.

APPENDIX 2 PERFORMANCE STATUS SCALES

STATUS	STATUS	STATUS
	ZUBROD-ECOG-WHO	
Normal, no complaints	0	Normal activity
Able to carry on normal activities Minor signs or symptoms of disease	1	Symptoms, but fully ambulatory
Cares for self. Unable to carry on normal activity or to do active work	2	Symptomatic, but in bed < 50% of the day.
Requires considerable assistance and frequent medical care	3	Needs to be in bed > 50% of the day, but not bedridden
Severely disabled. Hospitalization indicated though death non imminent	4	Unable to get out of bed
Dead	5	Dead

[redacted]

APPENDIX 3 PREPARATION AND ADMINISTRATION OF ELOTUZUMAB

Note: Subjects must be premedicated as described in Section 4.5.4 prior to elotuzumab infusion.

Dose Preparation Instructions

After dilution in normal saline, elotuzumab infusion must be completed within 8 hours if kept at room temperature (25 °C). In the United States and Puerto Rico, where a shortage of normal saline has been reported, dextrose 5% water (D5W) may be used. Normal saline is the preferred diluent and D5W should only be used if normal saline is not available. If a delay is anticipated after the dose has been diluted in normal saline, the prepared dose (properly identified) may be refrigerated at 2 °C to 8 °C for up to 24 hours. If stored under refrigerated conditions, the study drug solution should be equilibrated to room temperature (takes about 2 to 2.5 hours), and the container must be gently inverted to thoroughly mix the contents before administration. If the storage time limit is exceeded, the prepared dose solution must be discarded and the reason documented by the pharmacist in the study drug accountability records.

Elotuzumab will be administered to each subject as an IV infusion, using an automated infusion pump set at the appropriate rate according to the dose administration section (see Administration Instruction section below). The dose of elotuzumab will be calculated using the subject's predose weight on Day 1 of each cycle (the screening weight can be used for Cycle 1 dose calculation), and then added to 0.9% saline for infusion.

Reconstitute elotuzumab lyophilized study drug, as described in steps 1 to 5.

Step 1: For a 440 mg vial of lyophilized elotuzumab, draw 17 mL of Sterile Water for Injection (SWFI), USP into a syringe equipped with an 18-gauge or smaller needle.

Step 2: Remove the flip-top from the elotuzumab vial.

Step 3: Place the vial upright on a flat surface and, using standard aseptic techniques, insert the syringe needle into the vial through the center of the rubber stopper and deliver 17 mL (into the 20-mL vial containing 440 mg elotuzumab) SWFI, USP, into the vial. Slowly remove the syringe needle out of the vial. The final volume of the reconstituted solution is approximately 17.6 mL, which includes the volume displaced by the solid cake. The concentration of elotuzumab in the reconstituted solution is approximately 25 mg/mL.

Step 4: DO NOT SHAKE. Hold the vial upright and gently swirl the solution by rotating the vial to dissolve the lyophilized cake. Then gently invert the vial a few times in order to dissolve any powder that may be present on top of the vial or the stopper. Finally, hold the vial upright again and gently swirl the solution a few more times to dissolve any remaining particles. Avoid prolonged or vigorous agitation. DO NOT SHAKE.

Step 5: After the remaining solids are completely dissolved, allow the reconstituted solution to stand for 5 to 10 minutes.

It is acceptable to have small bubbles and/or foam around the edge of the vial. The reconstituted preparation results in a colorless to slightly yellow, clear to slightly opalescent solution containing approximately 25 mg/mL of elotuzumab.

Step 6: Once the reconstitution is completed, withdraw the calculated drug volume and further dilute with 100-500 ml of normal saline into an infusion bag (see Pharmacy Manual for additional details). The volume of saline or D5W can be adjusted so as not to exceed 5 mL/kg of patient weight at any given dose of elotuzumab. The resulting elotuzumab concentration must be from 1.0 mg/mL to 6.0 mg/mL. Elotuzumab solutions are compatible with polyvinyl chloride and polyolefin bags. Examples of such bags include Viaflo, MacoPharma Easyflex N, Macoflex N, B Braun Excel, and Braun Ecobag.

Drug volume will be calculated based on subject weight: For example, a subject receiving 10 mg/kg elotuzumab who weighs 80 kg on Day 1 [predose] will require 800 mg of study drug for infusion. Withdraw 32 mL of elotuzumab (25 mg/mL) from 2 vials and add to an infusion bag already containing 230 mL saline, for a total of 262 mL to be infused.

Similarly, an 80 kg subject receiving 20 mg/kg elotuzumab [predose] will require 1600 mg of study drug for infusion. Withdraw 64 mL of elotuzumab (25 mg/mL) from 4 vials and add to an infusion bag already containing 340 mL saline, for a total of 404 mL to be infused.

Use a new sterile needle for withdrawing solution from each vial.

The same vial must not be used to prepare elotuzumab for more than one subject. Used elotuzumab vials will be stored until study drug accountability has been completed by the BMS designee, and destruction or return is authorized. Used vials do not need to be refrigerated.

Note: Subjects must be premedicated as described in Section 4.5.4 prior to elotuzumab infusion.

Administration Instructions

The **first dose** of elotuzumab will be administered following premedications (described in Section 4.5.4) to each subject as an IV infusion, using an automated infusion pump set at an initial rate of 0.5 mL per minute (30 mL/hour). If the subject does not have an infusion reaction within 30 minutes, escalate the infusion rate by 0.5 mL per minute. If the subject still does not have an infusion reaction within 30 minutes, escalate the infusion rate to a **maximum of 2 mL** per minute (120 mL/hour). If a subject experiences a Grade ≥ 2 infusion reaction, the infusion must be interrupted. Please refer to Section 4.5.5.1 for detailed information on the management of infusion reaction and re-initiation of infusion.

The **second dose** of elotuzumab must be initiated at an infusion rate of **3 mL** per minute if no infusion reactions were observed with the first elotuzumab infusion. If the subject does not experience an infusion reaction during the first 30 minutes of the second dose of elotuzumab, escalate the infusion rate to 4 **mL** per minute.

The **third dose** of elotuzumab must be initiated at an infusion rate of **5 mL** per minute if no infusion reactions were reported with the second elotuzumab infusion.

The **fourth and subsequent doses** of elotuzumab must be initiated at an infusion rate of **5 mL** per minute if no infusion reactions were reported.

Elotuzumab Infusion Rate

The elotuzumab infusion rate will be increased gradually to a maximum of 5 mL/min as presented in Table 1. Table 1 represents an example for an 80 kg subject receiving 10mg/kg dose. The total volume varies according to the subject weigh and the elotuzumab administered dose.

Table 1, Appendix 3: Elotuzumab Infusion Rate Plan

Infusion Rate	Duration of infusion	Volume delivered	Volume remaining
Cycle 1 Dose 1	**Approximate Total Duration: 2hrs 50min**		**262 mL***
0.5 mL/min	30 min	15 mL	247 mL
1 mL/min	30 min	30 mL	217 mL
2 mL/min	110 min	217 mL	0 mL
Cycle 1 Dose 2	**Approximate Total Duration: 1hrs 13min**		**262 mL**
3 mL/min	30 min	90 mL	172 mL
4 mL/min	43 min	172 mL	0 mL
Cycle 1 Dose 3 and 4	**Approximate Total Duration: 53min**		262 mL
5 mL/min	53 min	262 mL	0 mL
Cycle 2 +	**Approximate Total Duration: 53min**		**262 mL**
5 mL/min	53 min	262 mL	0 mL

* Volume for 80 kg subject. Total volume varies according to the subject weight.

Please note that infusion rate increase to the next higher level only if no infusion reactions encountered.

If a subject experiences a Grade ≥ 2 infusion reaction, the infusion must be interrupted. Please refer to Section 4.5.5.1 for detailed information on the management of infusion reaction and re-initiation of infusion. If a subject experiences a Grade ≤ 3 elotuzumab infusion reaction that has resolved to Grade ≤ 1, subsequent infusion rate of elotuzumab should be escalated in a stepwise fashion (0.5 mL every 30 minutes as per Section 4.5.5.1).

1. Administer through a low-protein-binding 0.22 - micrometer or smaller in-line filter (placed as proximal to the subject as is practical). Prime the infusion line with study drug before starting the infusion.
2. Set the IV pump to deliver the infusion at the rate of 0.5 mL per minute (including the drug in the line). The total time of infusion will vary depending upon the maximum tolerated mL/min infusion rate as discussed above.
3. Record every time the infusion is started and stopped and the reason why the start and stop occurred.
4. Monitor the IV setup and the subject's IV site frequently during infusion, checking for the correct infusion rate and IV site infiltration.
5. Ensure that the full volume of elotuzumab is infused.

After elotuzumab has been infused from the line, discontinue the infusion, disconnect the IV tubing, and dispose of materials appropriately according to the facility's standard procedure.

Note: Subjects must be premedicated as described in Section 4.5.4 prior to elotuzumab infusion.

APPENDIX 4 DEFINITIONS OF RESPONSE AND PROGRESSION CRITERIA (MODIFIED FROM IMWG)

Response Subcategory	Response Criteria[a]
Stringent Complete Response (sCR)	CR, as defined below, plus the following: Normal FLC ratio[b] and absence of clonal cells[c] in bone marrow by immunohistochemistry or immunofluorescence.
Complete Response (CR)[b]	Negative immunofixation of serum and urine and disappearance of any soft tissue plasmacytomas, and < 5% plasma cells in bone marrow.
Very Good Partial Response (VGPR)	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-protein level plus urine M-protein level < 100 mg per 24 hour.
Partial Response (PR)	≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hour. If serum and urine M-protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. In addition to the above criteria, if present at baseline, ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
Minor (Minimal) Response (MR)	25-49% reduction of serum M-protein and reduction in 24-hour urine M-protein by 50-89%, which still exceeds 200 mg per 24 hours. In addition, if present at baseline, 25-49% reduction in the size of soft tissue plasmacytomas is also required. No increase in the size or number of lytic bone lesions (development of compression fracture does not exclude response).
Stable Disease (SD)	Not meeting criteria for CR, VGPR, PR, MR, or progression.
Progressive disease	Any of the following: • Increase of 25% from lowest response value in any one or more of the following: 1. Serum M-component (absolute increase must be ≥ 0.5 g/dL)[d] and/or 2. Urine M-component (absolute increase must be ≥ 200 mg per 24 h) and/or 3. Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL) 4. Bone marrow plasma cell percentage (absolute % must be ≥ 10%) • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcemia (corrected serum calcium > 11.5 mg/100 mL) that can be attributed solely to the plasma cell proliferative disorder

[a] All response categories require 2 consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed.

[b] Note clarification to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients is defined as a normal FLC ratio of 0.26-1.65 in addition to CR criteria listed above. VGPR in such patients is defined as a > 90% decrease in the difference between involved and uninvolved FLC levels.

[c] Presence or absence of clonal cells is based upon the κ/λ ratio. An abnormal κ/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of > 4:1 or < 1:2.

[d] For progressive disease, serum M-component increase of ≥ 1 g/dL is sufficient to define progression if starting M-component is ≥ 5 g/dL

APPENDIX 5 THE INTERNATIONAL STAGING SYSTEM (ISS) FOR MULTIPLE MYELOMA

Stage	Criteria	Median Survival (months)
Stage I	Serum β2-microglobulin < 3.5 mg/L Serum albumin ≥ 3.5 g/dL	62
Stage II	Not stage I or III (There are two categories for stage II) serum β2-microglobulin < 3.5 mg/L but serum albumin < 3.5 g/dL OR β2-microglobulin 3.5 to < 5.5 mg/L irrespective of the serum albumin level	44
Stage III	Serum β2-microglobulin ≥ 5.5 mg/L	29

Greipp PR, San Miguel JF, Brian GM, Durie JJ, Crowley BB, Blade J, Boccadoro J, Child A, Avet-Loiseau H, Kyle RA, Laheuerta JJ, Ludwig H, Morgan G, Powles R, Shimizu K, Shustik C, Sonneveld P, Tosi P, Turesson I, Westin J. International Staging System for Multiple Myeloma. J Clin Oncology 2005 23:3412-3420.

APPENDIX 6 POMALIDOMIDE PREGNANCY RISK PREVENTION PLAN

Appendix 5 only applies to subjects receiving clinical supply of pomalidomide.

Subjects receiving commercial supply of pomalidomide will follow the Pomalyst ® REMS program.

1 PREGNANCY PREVENTION RISK MANAGEMENT PLANS

1.1 Pomalidomide (CC-4047) Pregnancy Prevention Risk Management Plan

1.1.1 Pomalidomide Pregnancy Risk Minimization Plan for Celgene Clinical Trials

The following Pregnancy Risk Minimization Plan documents are included in this Appendix:

1) Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods (Section 1.1.1.1);
2) Pomalidomide Education and Counselling Guidance Document (Section 1.1.1.2);
3) Pomalidomide Information Sheet (Section 1.1.1.1).

1. The Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods document (Section 1.1.1.1) provides the following information:
    - Potential risks to the fetus associated with pomalidomide exposure
    - Definition of Female of Childbearing Potential (FCBP)
    - Pregnancy testing requirements for patients receiving Pomalidomide who are females of childbearing potential
    - Acceptable birth control methods for both female of childbearing potential and male patients receiving pomalidomide in the study
    - Requirements for counselling of all study patients receiving pomalidomide about pregnancy precautions and the potential risks of fetal exposure to pomalidomide
2. The Pomalidomide Education and Counselling Guidance Document (Section 1.1.1.2) must be completed and signed by either a trained counsellor or the Investigator at the participating clinical center prior to each dispensing of pomalidomide study treatment. A copy of this document must be maintained in the patient records.
3. The Pomalidomide Information Sheet (Section 1.1.1.1) will be given to each patient receiving pomalidomide study therapy. The patient must read this document prior to starting pomalidomide study treatment and each time they receive a new supply of study drug.

1.1.1.1 Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods

Risks Associated with Pregnancy

Pomalidomide was found to be teratogenic in a developmental study in rabbits. 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.

Criteria for females of childbearing potential (FCBP)

This protocol defines a female of childbearing potential as a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

Counselling

For a female of childbearing potential, pomalidomide is contraindicated unless all of the following are met (ie, all females of childbearing potential must be counselled concerning the following risks and requirements prior to the start of pomalidomide study therapy):

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 28 days before starting study treatment, throughout the entire duration of study treatment, dose interruption and 28 days after the end of study treatment
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence the study treatment as soon as study drug is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing based on the frequency outlined in this protocol (Section 1.1.1.1)
- She acknowledges that she understands the hazards and necessary precautions associated with the use of pomalidomide

The investigator must ensure that females of childbearing potential:

- Comply with the conditions for pregnancy risk minimization, including confirmation that she has an adequate level of understanding
- Acknowledge the aforementioned requirements

For a female NOT of childbearing potential, pomalidomide is contraindicated unless all of the following are met (ie, all females NOT of childbearing potential must be counselled concerning the following risks and requirements prior to the start of pomalidomide study therapy):

- She acknowledges that she understands the hazards and necessary precautions associated with the use of pomalidomide

The effect of pomalidomide on spermatogenesis is not known and has not been studied. Therefore, male patients taking pomalidomide must meet the following conditions (ie, all males must be counselled concerning the following risks and requirements prior to the start of pomalidomide study therapy):

- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a female of childbearing potential
- Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or a female of childbearing potential.

Contraception

Females of childbearing potential (FCBP) enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual contact during the following time periods related to this study: 1) for at least 28 days before starting study drug; 2) while participating in the study; 3) dose interruptions; and 4) for at least 28 days after study treatment discontinuation.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. FCBP must be referred to a qualified provider of contraceptive methods if needed. The following are examples of highly effective and additional effective methods of contraception:

- Highly effective methods:
  - → Intrauterine device (IUD)
  - → Hormonal (birth control pills, injections, implants)
  - → Tubal ligation
  - → Partner's vasectomy
- Additional effective methods:
  - → Male condom
  - → Diaphragm
  - → Cervical Cap

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking pomalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception the patient should

switch to another one of the effective methods listed above. The risk of venous thromboembolism continues for 4−6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.

Pregnancy testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for females of childbearing potential, including females of childbearing potential who commit to complete abstinence, as outlined below.

Before starting study drug

Female Patients:

FCBP must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting study drug. The first pregnancy test must be performed within 10-14 days prior to the start of study drug and the second pregnancy test must be performed within 24 hours prior to the start of study drug. The patient may not receive study drug until the study doctor has verified that the results of these pregnancy tests are negative.

Male Patients:

Must practice complete abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 28 days following study drug discontinuation, even if he has undergone a successful vasectomy.

During study participation and for 28 days following study drug discontinuation

Female Patients:

- → FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study discontinuation, and at day 28 following study drug discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study discontinuation, and at days 14 and 28 following study drug discontinuation.
- → At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control.
- → Counselling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- → If pregnancy or a positive pregnancy test does occur in a study patient, study drug must be immediately discontinued.

- → Pregnancy testing and counselling must be performed if a patient misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Study drug treatment must be discontinued during this evaluation.
- → Females must agree to abstain from breastfeeding during study participation and for at least 28 days after study drug discontinuation.

Male Patients:

- → Counseling about the requirement for complete abstinence or condom use during sexual contact with a pregnant female or a female of childbearing potential and the potential risks of fetal exposure to pomalidomide must be conducted at a minimum of every 28 days.
- → If pregnancy or a positive pregnancy test does occur in the partner of a male study patient during study participation, the investigator must be notified immediately.

Additional precautions

- → Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to the study doctor at the end of treatment.
- → Patients should not donate blood during therapy and for at least 28 days following discontinuation of study drug.
- → Male patients should not donate semen or sperm during therapy or for at least 28 days following discontinuation of study drug.
- → Only enough study drug for one cycle of therapy may be dispensed with each cycle of therapy.

1.1.1.2 Pomalidomide Education and Counselling Guidance Document

To be completed prior to each dispensing of study drug.

Protocol Number: _____

Patient Name (Print): _____ DOB: _____/_____/_____ (mm/dd/yyyy)

(Check the appropriate box to indicate risk category)

Female:

If female, check one:

FCBP (Female of childbearing potential): sexually mature female who: 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time during the preceding 24 consecutive months)

NOT FCBP

Male:

Do Not Dispense study drug if:

→ The patient is pregnant.
→ No pregnancy tests were conducted for a FCBP.
→ The patient states she did not use TWO reliable methods of birth control (unless practicing complete abstinence of heterosexual contact) [at least 28 days prior to therapy, during therapy and during dose interruption].

FCBP:

1. I verified that the required pregnancy tests performed are negative.
2. I counselled FCBP regarding the following:
   - Potential risk of fetal exposure to pomalidomide: If pomalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid pregnancy while taking pomalidomide. The teratogenic potential of pomalidomide in humans cannot be ruled out. FCBP must agree not to become pregnant while taking pomalidomide.
   - Using TWO reliable methods of birth control at the same time or complete abstinence from heterosexual contact [at least 28 days prior to therapy, during therapy , during dose interruption and 28 days after discontinuation of study drug].
   - That even if she has amenorrhea she must comply with advice on contraception

- Use of one highly effective method and one additional method of birth control AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:
  - ♦ Highly effective methods:
    - Intrauterine device (IUD)
    - Hormonal (birth control pills, injections, implants)
    - Tubal ligation
    - Partner's vasectomy
  - ♦ Additional effective methods:
    - Male condom
    - Diaphragm
    - Cervical Cap
- Pregnancy tests before and during treatment, even if the patient agrees not to have reproductive heterosexual contact. Two pregnancy tests will be performed prior to receiving study drug, one within 10-14 days and the second within 24 hours of the start of study drug.
- Frequency of pregnancy tests to be done:
- Every week during the first 28 days of this study and a pregnancy test every 28 days during the patient's participation in this study if menstrual cycles are regular or every 14 days if cycles are irregular.
- If the patient missed a period or has unusual menstrual bleeding.
- When the patient is discontinued from the study and at day 28 after study drug discontinuation if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at days 14 and 28 after study drug discontinuation.
- Stop taking study drug immediately in the event of becoming pregnant and to call their study doctor as soon as possible.
- NEVER share study drug with anyone else.
- Do not donate blood while taking study drug and for 28 days after stopping study drug.
- Do not breastfeed a baby while participating in this study and for at least 28 days after study drug discontinuation.
- Do not break, chew, or open study drug capsules.
- Return unused study drug to the study doctor.

3. Provide Pomalidomide Information Sheet to the patient.

FEMALE NOT OF CHILDBEARING POTENTIAL (NATURAL MENOPAUSE FOR AT LEAST 24 CONSECUTIVE MONTHS, A HYSTERECTOMY, OR BILATERAL OOPHORECTOMY):

I counselled the female NOT of childbearing potential regarding the following:

→ Potential risk of fetal exposure to pomalidomide (Refer to item #2 in FCBP)
→ NEVER share study drug with anyone else.
→ Do not donate blood while taking study drug and for 28 days after stopping study drug.
→ Do not break, chew, or open study drug capsules
→ Return unused study drug capsules to the study doctor.

Provide Pomalidomide Information Sheet to the patient.

MALE:

I counselled the Male patient regarding the following:

→ Potential study drug fetal exposure to pomalidomide (Refer to item #2 in FCBP).
→ To engage in complete abstinence or use a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or a female of childbearing potential, while taking study drug, during dose interruptions and for 28 days after stopping study drug.
→ Males should notify their study doctor when their female partner becomes pregnant and female partners of males taking study drug should be advised to call their healthcare provider immediately if they get pregnant
→ NEVER share study drug with anyone else.
→ Do not donate blood while taking study drug and for 28 days after stopping study drug.
→ Do not donate semen or sperm while taking study drug and for 28 days after stopping study drug.
→ Do not break, chew, or open study drug capsules.
→ Return unused study drug capsules to the study doctor.

Provide Pomalidomide Information Sheet to the patient.

Investigator/Counsellor Name (Print): _____
(circle applicable)

Investigator/Counsellor Signature: _____ Date: _____/_____/_____
(circle applicable)

Maintain a copy of the Education and Counselling Guidance Document in the patient records.

1.1.1.3 Pomalidomide Information Sheet

FOR PATIENTS ENROLLED IN CLINICAL RESEARCH STUDIES

Please read this Pomalidomide Information Sheet before you start taking study drug and each time you get a new supply. This Pomalidomide Information Sheet does not take the place of an informed consent to participate in clinical research or talking to your study doctor or healthcare provider about your medical condition or your treatment.

What is the most important information I should know about pomalidomide?

Pomalidomide may cause birth defects (deformed babies) or death of an unborn baby. Pomalidomide is similar to the medicine thalidomide. It is known that thalidomide causes life-threatening birth defects. Pomalidomide has not been tested in pregnant women but may also cause birth defects. Pomalidomide was found to cause birth defects when tested in pregnant rabbits. **If you are a female who is able to become pregnant:**

- → **Do not take study drug if you are pregnant or plan to become pregnant**
- → **You must either not have any sexual relations with a man or use two reliable, separate forms of effective birth control at the same time:**
  - → for 28 days before starting study drug
  - → while taking study drug
  - → during dose interruptions of study drug
  - → for 28 days after stopping study drug
- → **You must have pregnancy testing done at the following times:**
  - → within 10 – 14 days and again 24 hours prior to the first dose of study drug
  - → weekly for the first 28 days
  - → every 28 days after the first month or every 14 days if you have irregular menstrual periods
  - → if you miss your period or have unusual menstrual bleeding
  - → 28 days after the last dose of study drug (14 and 28 days after the last dose if menstrual periods are irregular)
- → **Stop taking study drug if you become pregnant during treatment**
  - → If you suspect you are pregnant at any time during the study, you must stop study drug immediately and immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene Corporation.
- → **Do not breastfeed while taking study drug**
- → **The study doctor will be able to advise you where to get additional advice on contraception.**

If you are a female not of childbearing potential:

In order to ensure that an unborn baby is not exposed to pomalidomide, your study doctor will confirm that you are not able to become pregnant.

If you are a male:

The effect of pomalidomide on sperm development is not known and has not been studied. The risk to the fetus in females of child bearing potential whose male partner is receiving pomalidomide is unknown at this time.

Male patients (including those who have had a vasectomy) must either **not have any sexual relations with a pregnant female or a female who can become pregnant,** or must use a condom during sexual contact with a pregnant female or a female that can become pregnant:

- While you are taking study drug
- During dose interruptions of study drug
- For 28 days after you stop taking study drug

Male patients should not donate sperm or semen while taking study drug and for 28 days after stopping study drug.

If you suspect that your partner is pregnant any time during the study, you must immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene Corporation. Your partner should call their healthcare provider immediately if they get pregnant.

Restrictions in sharing study drug and donating blood:

Do not share study drug with other people. It must be kept out of the reach of children and should never be given to any other person.

Do not donate blood while you take study drug and for 28 days after stopping study drug.

Do not break, chew, or open study drug capsules.

You will be supplied with no more than one cycle of study drug

Return unused study drug capsules to your study doctor.

Additional information is provided in the informed consent form and you can ask your study doctor for more information.