Official Title of Study:

An Open-Label, Randomized Phase 3 Trial of Combinations of Nivolumab, Pomalidomide and Dexamethasone in Relapsed and Refractory Multiple Myeloma

(CheckMate 602: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 602)

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CLINICAL PROTOCOL CA209602

An Open-Label, Randomized Phase 3 Trial of Combinations of Nivolumab, Pomalidomide and Dexamethasone in Relapsed and Refractory Multiple Myeloma

(CheckMate 602: **CHECK**point pathway and nivolu**MA**b clinical **T**rial **E**valuation **602**)

Revised Protocol Number: 03

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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	12-Nov-2018	Major changes: • Enrollment into the study was stopped as of 23-August-2018, due to the results of the futility analysis performed on 12-April-2018. • All efficacy assessments will be based on the investigator evaluation rather than Independent Review Committee (IRC). • Bone marrow aspirate collection time-points and samples are reduced; • [redacted] • Update of Appendix 3 Definitions of Response and Progression criteria, Appendix 5 Nivolumab Management Algorithm and Appendix 6 Pomalidomide Pregnancy Risk Prevention Plan.
Revised Protocol 02	22-May-2018	Major changes: • Incorporates changes required by the FDA per the partial clinical hold based on safety concerns from pembrolizumab studies, as well as study design and objective changes to reflect endpoints adequacy in light of these safety concerns. [redacted] • Revision of efficacy assessments (Appendix III) to align with the current International Myeloma Working Group (IMWG) guidance.
Revised Protocol 01	27-Dec-2016	Incorporates changes from Amendment 03
Amendment 03	27-Dec-2016	Incorporates Investigator Brochure updates, Data Monitoring Committee and Investigator Meeting feedback, [redacted] and allowance for BMS-provided pomalidomide
Administrative Letter 03	14-Sep-2016	[redacted] to add clarity to eligibility criteria regarding prior lines of therapy
Administrative Letter 02	30-Mar-2016	In response to Schulman IRB to bring sperm donation language into consistency
Administrative Letter 01	14-Mar-2016	[redacted]
Original Protocol	06-Jan-2016	NA

OVERALL RATIONALE FOR THE REVISED PROTOCOL 03

As of 23-August-2018, enrollment into the CA209602 study was permanently closed due to insufficient benefit observed based on the interim futility analysis of progression free survival (PFS). Subjects randomized to the nivolumab+pomalidomide (NPd) or nivolumab+elotuzumab +pomalidomide (NEPd) arms may continue treatment based on investigator's judgement of continued clinical benefit. The study will close after all enrolled subjects complete safety follow-up (i.e., 100 days after the last subject has discontinued study treatment). To align with this change, study assessments have been modified: all efficacy assessments will now be based on investigator evaluation rather than by an independent review committee (IRC), bone marrow aspirate collection time-points and samples are reduce [redacted] as of Revised Protocol 03.

Additional changes include update of the Nivolumab Management Algorithms (Appendix 5) and Pomalidomide Pregnancy Risk Prevention Plan (Appendix 6) and a minor modification of Appendix 3: Definitions of Response and Progression Criteria.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 03

Section Number & Title	Description of Change	Brief Rationale
• Synopsis, Objectives, Study Assessments, Statistical Considerations	All efficacy assessments will be based on investigator evaluation rather than by IRC.	An independent review committee (IRC) had been set up to review efficacy data. However, after enrollment was discontinued, the Sponsor decided to discontinue efficacy assessment by IRC All efficacy objectives and endpoints are now based on investigator assessment.
• Synopsis, Study Design Statistical Considerations • Section 1.7 Overall Benefit Risk Assessment • Section 3.1 Study Design and Duration	Text has been modified and/or new text added to describe end of enrollment into the study.	As of 23-August-2018, enrollment into the CA209602 study was permanently closed due to insufficient benefit observed based on the interim futility analysis of progression free survival (PFS). Subjects randomized to the NPd or NEPd arms may continue treatment based on investigator's judgement of continued clinical benefit.
• Section 3.5 Discontinuation of Subjects following any Treatment with Study Drug.	Corrected missing end of treatment criteria	Deleted in error in Revised Protocol 02.
• Section 4.5.4.4.3 Nivolumab Dose Discontinuation	As of 23-August-2018, subjects may be discontinued at the investigator's discretion based on safety results from the interim analysis and subject's derived clinical benefit.	Subjects already enrolled in the study and randomized to the NPd or NEPd arms may continue treatment based on investigator's judgement of continued clinical benefit.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
• Section 5.1 Flow Chart/Time and Events Schedule: All Time and Event Tables in Section 5.1 • Section 5.4.2, Laboratory Assessments for Myeloma and Table 5.4.2-1 Bone Marrow Aspirate Samples [redacted]	Collection time points and samples obtained for bone marrow aspirate have been modified based on results of the futility analyses for PFS.	Modification of study assessments, based on the close in enrollment for this study.
• Section 5.1 Flow Chart/Time and Events Schedule: All Time and Event Tables in Section 5.1 • [redacted]	[redacted]	
[redacted]		

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
• Section 7 Data Monitoring Committee and Other External Committees	Text added to address change from Independent Review Committee to investigator evaluation for efficacy assessments.	An independent review committee (IRC) had been set up to review blinded efficacy data. However, after enrollment was discontinued, the Sponsor decided to discontinue efficacy assessment by IRC.
• Section 8, Statistical Considerations.	Section has been revised to align with all study changes previously described.	Alignment of protocol to 1) end of enrollment and 2) use of investigator assessments for all efficacy objectives/endpoints, replacing IRC.
• Appendix 3	Definitions of Response and progression criteria: minor adjustment to apply to study population The standard IMWG response criteria have been limited to the eligible patient population in the study.	Alignment with study population
• Appendix 5	Hepatic Adverse Event Management Algorithm: Footnote stating I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN has been removed.	Updated to align with nivolumab program standard.
• Appendix 6	Pomalidomide Pregnancy Risk Prevention Plan	Updated Version
Throughout the protocol	Editorial or formatting changes that do not impact protocol content.	

SYNOPSIS

Clinical Protocol CA209602

Protocol Title: An Open-Label, Randomized Phase 3 Trial of Combinations of Nivolumab, Pomalidomide and Dexamethasone in Relapsed and Refractory Multiple Myeloma

(CheckMate 602: **CHECK**point pathway and nivolu**MA**b clinical **T**rial **E**valuation **602**)

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): See **Study Schema** for details

Control Arm (Pd: Arm B):

Pomalidomide: 4 mg PO QD Days 1-21 of each 28-day cycle

Dexamethasone:

- Subjects ≤ 75 years old: 40 mg PO Days (1, 8, 15, and 22) of each cycle
- Subjects > 75 years old: 20 mg PO Days (1, 8, 15, and 22) of each cycle

Investigational Arm (N-Pd: Arm A):

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

Pomalidomide: 4 mg PO QD Days 1-21 of each 28-day cycle

Dexamethasone:

- Subjects ≤ 75 years old: 40 mg PO Days (1, 8, 15, and 22) of each cycle
- Subjects > 75 years old: 20 mg PO Days (1, 8, 15, and 22) of each cycle

Exploratory Arm (NE-Pd: Arm C): Enrollment closed per Revised Protocol 02

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

Elotuzumab:

- Cycles 1 - 2: 10 mg/kg IV Days 1, 8, 15, and 22 of each 28-day cycle
- Cycle 3 and 4: 10mg/kg IV Day 1 and 15 of each 28-day cycle
- Cycles 5 and beyond: 20 mg/kg IV Day 1 of each 28-day cycle

Pomalidomide: 4 mg PO QD Days 1-21 of each 28-day 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

A cycle is defined as 28 days. Treatment with study drug continues until disease progression, unacceptable toxicity, or subject meets other criteria for discontinuation of study drug outlined in Section 3.5.

Study Phase: 3

Research Hypothesis:. The addition of nivolumab to pomalidomide and dexamethasone will increase the clinical benefit represented by increased progression free survival (PFS) and higher response rate compared to pomalidomide and dexamethasone in subjects with relapsed and/or refractory multiple myeloma.

Objectives:

Primary Objectives

The primary objective is to compare progression free survival (PFS) between N-Pd and Pd arms, by investigator.

Secondary Objectives

- To estimate overall survival (OS) within N-Pd and Pd arms
- To assess the time to objective response (TTR) within N-Pd and Pd arms by investigator
- To assess the duration of objective response (DOR) within N-Pd and Pd arms by investigator
- To compare ORR between N-Pd and Pd arms, by investigator.

Exploratory Objectives

- To evaluate efficacy of NE-Pd in subjects with relapsed and/or refractory multiple Myeloma within NE-Pd arm through the assessment of ORR and PFS
- To evaluate efficacy of NE-Pd in subjects who crossed over from the control arm (Pd) to the exploratory arm (NE-Pd) through the assessment of ORR and PFS
- To assess safety and tolerability

[redacted]

Study Design:

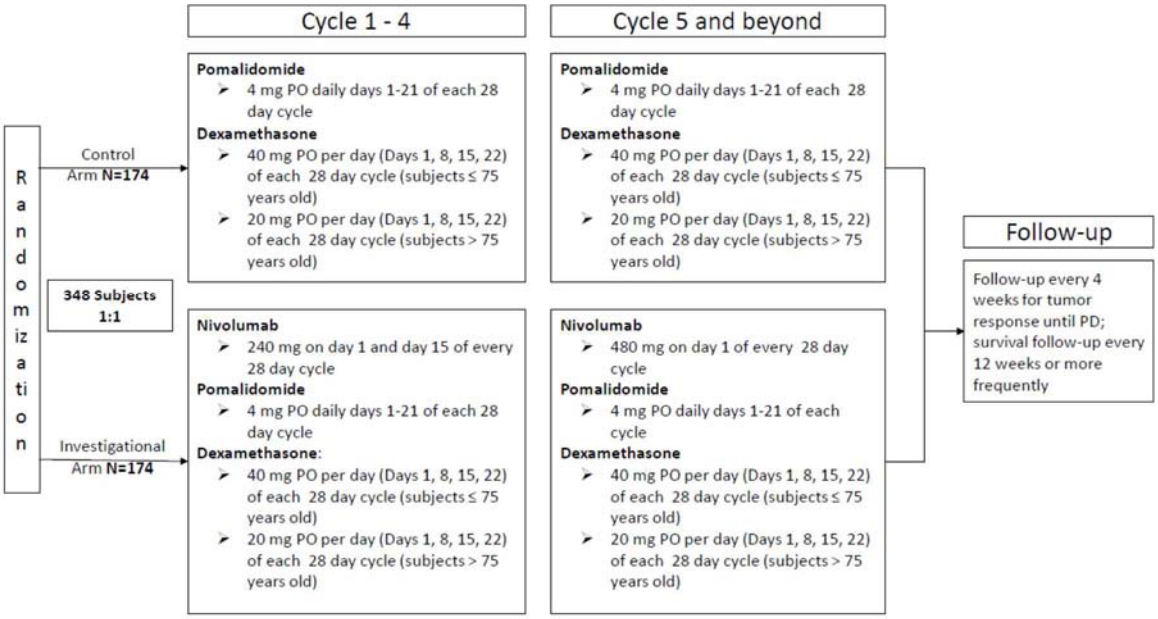
This is a phase 3 multicenter, randomized, open label study designed to evaluate the clinical benefit and safety of the combination therapy of Nivolumab, pomalidomide, and dexamethasone (N-Pd the investigational arm-armA), when compared to pomalidomide and dexamethasone (Pd; the control arm-arm B) in subjects with relapsed and/or refractory multiple myeloma (rrMM). Revised Protocol 01 included an exploratory third arm evaluating the clinical benefit and the safety of the combination therapy of elotuzumab, nivolumab, pomalidomide and dexamethasone (NE-Pd, the exploratory arm-arm C) in the same patient population. Additionally, subjects randomized to the Pd arm were allowed to cross over to this exploratory NE-Pd arm at the time of progression. Cross over was stopped as of 1 September 2017. Enrollment in the NE-Pd exploratory arm was stopped as of Protocol version 02 All subjects already randomized to the NE-Pd arm, or who crossed over from the Pd to the NE-Pd arm will continue on study as long as they have clinical benefit and do not meet the study discontinuation criteria.

Initially, the study was designed to enroll approximately 417 subjects for a total of 348 subjects to be randomized (assuming 20% screen failure rate) to N-Pd and Pd in a 1:1 ratio. Randomization was performed with the following stratification factors: a) number of lines of prior therapy (2 vs 3+); AND b) ISS stage (1-2 vs 3).

Subjects were to continue treatment as long as the subject has clinical benefit from the treatment and does not meet criteria for treatment discontinuation.

As of 23-August-2018, the further enrollment of CA209602 study was permanently closed due to the insufficient benefit observed based on the interim futility analysis of PFS. A total of 170 subjects were randomized into the study: 75 to NPd, 71 to Pd and 24 to NE-Pd arms. Subjects randomized to the NPd or NEPd arms may continue treatment based on investigator's judgement of continued clinical benefit. Study will be closed after all subjects complete safety follow-up (i.e., 100 days after the last subject has discontinued study treatment).

The study design schematic is presented below:



Study Population: Subjects who are diagnosed with refractory or relapsed multiple myeloma defined as:

1. Must have received ≥ 2 prior lines of therapy which must have included an immune modulatory drug (IMiD) and a proteasome inhibitor (PI) alone or in combination. Subject must have received at least 2 consecutive cycles of an IMiD and at least 2 consecutive cycles of a PI. The dose of the prior IMiD (eg, lenalidomide) to which the subject has relapsed or been refractory must be the induction dose and NOT a maintenance dose (Note: adjusted induction dose for intolerance reasons or for renal impairment is accepted).
2. Documented refractory or relapsed and refractory (R/R) multiple myeloma
3. Refractory (lack of response or progressed on or within 60 days of the last dose of treatment) to their last line of treatment. Lack of response is defined as not having achieved at least PR.[i]
4. Subjects must have failed treatment with a proteasome inhibitor and an IMID in one of the following ways:
    a. "Refractory" = Refractory (lack or response or progressed on treatment or within 60 days of the last dose of treatment, regardless of the achievement of initial response) to a proteasome inhibitor and an IMiD. Lack of response is defined as not having achieved at least PR.[i]

b. "Relapsed and refractory"= patients had achieved at least a partial response to previous treatment with proteasome inhibitor or IMiD or both but then progressed after 60 days of the last dose of treatment.

5. Have measurable disease
6. Meet all eligibility criteria in Section 3.3

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

Study Drug for CA209602		
Medication	**Potency**	**IP/Non-IP**
Nivolumab	100 mg (10 mg/mL)	IP
Elotuzumab	400mg/vial	IP
Pomalidomide Capsules	1 mg, 2 mg, 3 mg and 4 mg	Non-IP
Dexamethasone Tablets	2 mg and 4 mg & various strengths	Non-IP
Dexamethasone Solution	4 mg/mL, 8 mg/mL & various strengths	Non-IP

Study Assessments: Tumor response assessment by IMWG criteria will be evaluated during the trial for all randomized subjects. The primary endpoint PFS will be based on the investigator.

Statistical Considerations:

Sample Size:

In Revised Protocol 02, the planned sample size for this study was revised to approximately 348 randomized subjects randomized at a 1:1 ratio to N-Pd vs Pd. The sample size of the study accounts for the primary efficacy endpoint of PFS. PFS will be evaluated for treatment effect at the overall alpha level of 0.05 (two-sided) with 90% power with two interim analyses, with the first one for early futility and the second for efficacy.

The study requires at least 262 PFS events to ensure that a two-sided 5% type I error sequential test procedure with two interim analyses will have 90% power to detect a hazard ratio (HR) of 0.667, corresponding to a median PFS of 6 vs 4 months for the N-Pd and Pd arms, respectively.

On 23-August-2018, the Sponsor (BMS) decided to permanently discontinue enrollment based on insufficient clinical benefit observed at an interim futility analysis for PFS. A total of 170 subjects have been randomized in the study.

Endpoints:

Primary Endpoints:

The primary objective in the study will be measured by the primary endpoint PFS by investigator within the N-Pd and Pd arms.

Secondary Endpoints:

The secondary objectives in the study will be measured by

- OS
- ORR
- TTR
- DOR

Analyses:

PFS Analysis Timepoints

- At the time of PFS analyses, as assessed by investigator, the distribution of PFS in N-Pd group will be compared with the Pd arm via a two-sided, log-rank test stratified by prior lines of therapy and ISS stage at study entry. The hazard ratio (HR) and the corresponding 100x(1-adjusted alpha)% confidence interval (CI) will be estimated in a stratified Cox proportional hazards model using treatment as a single covariate.
- PFS curves, PFS medians with two-sided 95% CIs, and PFS rates at at select milestone with 95% CIs will be estimated using Kaplan-Meier methodology.

Analysis of OS

- At the time of PFS analyses, OS will be summarized by the Kaplan-Meier product limit method within each arm. Median values along with two-sided 95% CIs based on the log log transformation, will be calculated. Additional details of OS analysis will be included in the SAP

Analysis of ORR by investigator

- Investigator-determined ORR analyses will be conducted using a two sided Cochran Mantel Haenszel (CMH) test stratified by prior lines of therapy and ISS stage at study entry to compare N-Pd to Pd arm. Associated odds ratios and 95% CIs will be calculated. Additionally, ORRs and corresponding 95% exact CIs will be calculated using the Clopper Pearson method for N-Pd and Pd arms

Analysis of DOR and TTR

- DOR and TTR will be computed for subjects who achieve sCR, CR, VGPR, or PR as assessed by investigator according to modified IMWG criteria. Median values of DOR, along with two-sided 95% CI, will be calculated using KM product-limit method. Summary statistics of TTR will be provided. More detailed analysis of DOR and TTR will be described in the statistical analysis plan (SAP).

Details on the testing procedure will be described in SAP.

Safety Analysis

The safety analysis will be performed in all treated subjects. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 by treatment group. Adverse Events (AE), drug-related AEs, Serious Adverse Events (SAE) and drug-related SAEs will be tabulated using worst grade per NCI CTCAE v.4.0 criteria by system organ class and preferred term. On-study lab parameters including hematology, chemistry, liver function and renal function will be summarized using worst grade per NCI CTCAE v.4.0 criteria.

REFERENCES

[i] Rajkumar SV1, Harousseau JL, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood. 2011 May 5;117(18):4691-5. doi: 10.1182/blood-2010-10-299487

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1 INTRODUCTION AND STUDY RATIONALE

1.1 Multiple Myeloma

Among hematologic malignancies, multiple myeloma (MM) is the second most prevalent blood cancer after non-Hodgkin lymphoma, representing 10% of hematologic malignancies. In the United States there are an estimated 26,850 new cases and 11,240 deaths predicted for 2015[1]. The incidence of MM in Europe is 4.5 to 6.0/100,000/year and the mortality is 4.1/100,000/year[1]. The incidence of MM increases with advancing age and the median age of diagnosis in the US is 70 years[1] and in Europe between 65 and 70 years[1].

MM is a germinal center-derived tumor with mainly a post-switch B-cell phenotype characterized by extensive gene hypermutation in a pattern suggesting antigen selection. It is the most frequent primary neoplasm of the bone marrow. Pathologically, it stems from an expansion of a single clone of abnormal terminally differentiated B cells (plasma cells) that produce a monoclonal immunoglobulin (M-protein) and replace the normal bone marrow, leading to hypofunctioning of the bone marrow, osteolytic bone lesions, hypercalcemia, and renal disease[2].

1.2 Current Treatment Regimens and Unmet Medical Need

Currently approved treatments commonly used for patients with relapsed / refractory MM include proteasome inhibitor (PI) based therapies (eg, bortezomib, carfilzomib), immune modulatory drug (IMiD) based therapies (thalidomide, lenalidomide, or pomalidomide) and histone deacetylase inhibitors.[3,4] More recently an oral proteasome inhibitor (ixazomib) as well as new drug classes, elotuzumab (anti-SLAMF7 monoclonal antibody) and daratumumab (anti-CD38 monoclonal antibody) have also been approved for treatment of rrMM. There is no cure and current therapies can only slow disease progression, prolong survival, and minimize symptoms. 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] Multiple myeloma is associated with morbidity and mortality, thus reflecting a significant unmet medical need.

1.3 Study Rationale

1.3.1 Rationale for Nivolumab Development in Multiple Myeloma

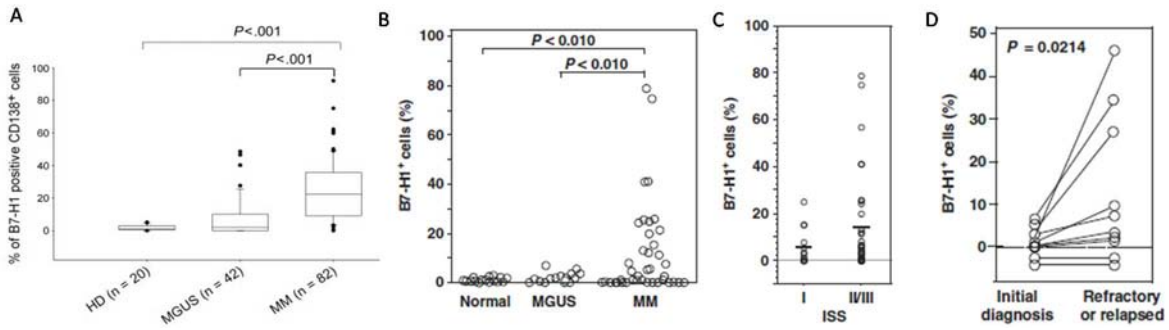
Multiple myeloma (MM) is characterized by immune suppression in the bone marrow (BM) microenvironment which supports immune evasion and a growth advantage for malignant plasma cells. The nature of this suppression involves many cell types that have been implicated in inhibiting immune responses to control myeloma cell growth. In part, PD-L1 has been shown to play a role in mediating inhibition of both adaptive and innate immunity in the bone marrow milieu of MM patients. As PD-L1 is over-expressed on MM cells and other cells in the BM microenvironment from MM patients, its receptor PD-1 is also found over-expressed on both CD8+ T and some NK cell subsets. Therefore PD-L1 mediated suppression of PD1+ T and NK cells is one potential mechanism in place to confer immune escape.

PD-L1 in MM

1) PD-L1 on myeloma cells:

While PD-L1 is seldom found on normal plasma cells, myeloma cells frequently express PD-L1 and this expression is further enhanced when cultured with bone marrow stromal cells (BMSCs).[6,7,8] Limited data to date also suggests that PD-L1 expression on myeloma cells may be increased with disease burden, stage and at time of relapse suggesting a possible mechanism for immune escape from current therapies.[9]

Figure 1.3.1-1: PD-L1 expression in myeloma cells.



a., b: PD-L1 expression is increased on BM myeloma cells in MM patients

c: PD-L1 expression on BM plasma cells may be increased with disease stage

d: increase in PD-L1 on BM plasma cells associated with progression (within individual patients).[6,9]

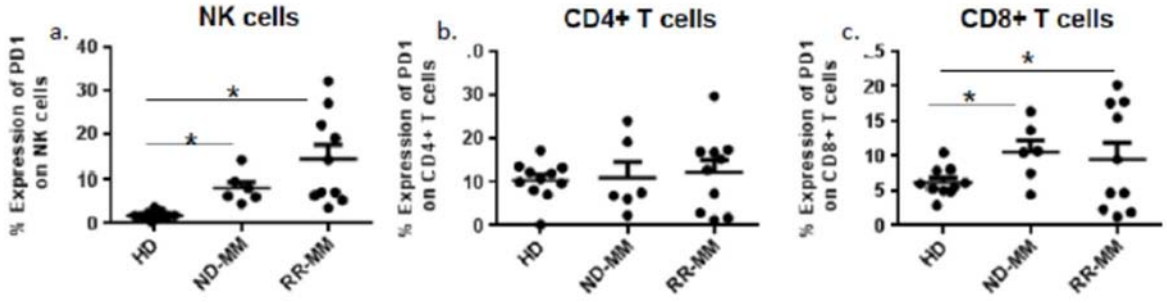
2) PD-L1 on immune cells in MM:

PD-L1 can also mediate suppression of immune effector function through its expression on other cells in the BM of MM patients. PD-L1 is found to be over-expressed on both MDSCs (myeloid-derived suppressor cells) and pDCs (plasmacytoid dendritic cells) in the BM of MM patients and this expression has been shown to drive suppression of both CD8+ T and NK and cell responses in vitro.[8,10]

PD-1 in MM

PD-1 plays a role in maintaining T cell homeostasis and its expression on T cells is generally associated with an antigen-activated or an exhausted phenotype. Increased frequency of PD-1 + T cell subsets have been reported in many tumor types including MM.[8,11] Increased frequency of PD1+ NK cells have also been observed in the BM of MM patients.[8,12] Therefore expression of PD-1 on cytolytic immune cells such as CD8+ T and NK cells (Figure 1.3.1-2) represents a possible mechanism of how PD-L1-expressing tumor cells and suppressive immune cells can inhibit effector cell function conferring immune escape and growth of myeloma cells.[12]

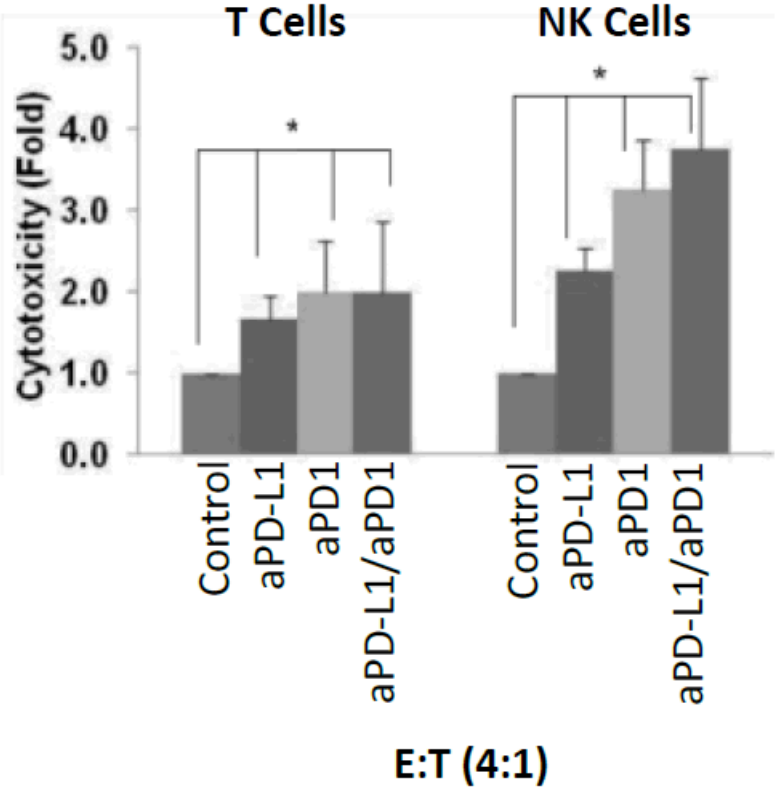
Figure 1.3.1-2: Increased frequency of PD-1 expression in BM effector cells.[8]



Effects of PD-1 and/or PD-L1 blockade in enhancing immune cell function and killing of myeloma cells.

The PD-1/PD-L1 axis imposes an inhibitory mechanism to reduce effector cell function and killing of myeloma cells. This state of inhibition is mediated in part through tumor cell PD-L1 suppression of effector cells. Blocking antibodies targeting PD-1 or PD-L1 (or both) can directly enhance effector cell function and killing of myeloma cells in vitro (Figure 1.3.1-3). Additionally, PD-1/PD-L1-blocking antibodies can inhibit suppressive mechanisms in vitro mediated by PD-L1+ MDSCs and pDCs, and overcome bone marrow stromal cell (BMSC)-induced growth of myeloma cells.[8]

Figure 1.3.1-3: **PD-1/PD-L1 blockade enhances immune effector cell-mediated anti-myeloma responses in samples from BM of MM patients. Labeled target CD138+ MM cells cultured with autologous T or NK cells +/- aPD1, a-PD-L1 or the combination[8]**



Nivolumab is a fully human, IgG4 (κ) isotype mAb that binds PD-1 on activated immune cells and disrupts engagement of the receptor with its ligands PD-L1(B7-H1/CD274) and PD-L2(B7-DC/CD273), thereby abrogating inhibitory signals and augmenting the host antitumor response.

Nivolumab has demonstrated clinical activity as monotherapy in subjects with a variety of malignancies including lung, melanoma, renal cell carcinoma and in lymphomas, responses have been reported for diffuse large B-cell lymphoma, follicular lymphoma, head and neck cancer, and Hodgkin's lymphoma.

Approximately 8,000 subjects have received nivolumab monotherapy in single- or multiple-dose Phase 1/2/3 studies or studies with nivolumab in combination with other therapeutics (ipilimumab, cytotoxic chemotherapy, anti angiogenics, and targeted therapies). The safety profile is generally consistent across completed and ongoing clinical trials, with no maximum tolerated dose (MTD) reached at any monotherapy dose tested up to 10 mg/kg. There was no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. The safety profile of nivolumab combination therapy varies with the agent combined with nivolumab, but is generally consistent with the safety

profiles observed with either agent alone and, in some cases, the frequency of AEs may be greater than that observed with either agent alone. For nivolumab monotherapy and combination therapy, most high-grade events were manageable with use of corticosteroids and/or hormone replacement therapy.

Nivolumab is indicated for the treatment of patients with unresectable or metastatic melanoma as both a single agent and in combination with ipilimumab. Nivolumab is also approved for non-small cell lung cancer following failure on or after platinum based therapy, as well as for advanced renal cell carcinoma following treatment with an anti-angiogenic therapy. Opdivo® (nivolumab) is approved for use in multiple countries including the United States (US Dec 2014), the European Union (EU June 2015) and Japan (Jul 2015).

1.3.1.1 Rationale for Nivolumab dose and frequency

The nivolumab dose of 240 mg every 2 weeks (Q2W) was selected based on clinical data and modeling and simulation approaches using population PK (PPK) and exposure-response analyses of data from studies in multiple tumor types (melanoma, non-small-cell lung cancer [NSCLC], and renal cell carcinoma [RCC]) where body weight normalized dosing (mg/kg) has been used.

PPK analyses have shown that the PK of nivolumab is linear with proportional exposure over a dose range of 0.1 to 10 mg/kg, and no differences in PK across ethnicities and tumor types were observed. Nivolumab clearance and volume of distribution were found to increase as the body weight increases, but less than the proportional with increasing weight, indicating that mg/kg dosing represents an over-adjustment for the effect of body weight on nivolumab PK. The PPK model previously developed using data from NSCLC subjects has recently been updated, using data from 1544 subjects from 7 studies investigating nivolumab in the treatment of melanoma, NSCLC, and RCC. In this dataset, the median (minimum - maximum) weight was 77 kg (35 kg - 160 kg) and thus, an approximately equivalent dose of 3 mg/kg for an 80 kg subject, nivolumab 240 mg Q2W was selected for future studies. To predict relevant summary exposures of nivolumab 240 mg Q2W, the PPK model was used to simulate nivolumab 3 mg/kg Q2W and 240 mg Q2W. In the simulations, the simulated patient populations consisted of 1000 subjects per treatment arm randomly sampled from aforementioned pooled database of cancer subjects. Because no differences in PK were noted across ethnicities and tumor types, these simulated melanoma and NSCLC data will be applicable to subjects with other tumor types. The simulated measure of exposure of interest, time-averaged concentrations (Cavgss) for 240 mg Q2W are predicted to be similar for all subjects in reference to 80 kg subjects receiving 3 mg/kg Q2W.

Nivolumab is safe and well tolerated up to 10 mg/kg Q2W dose level. Adverse events have been broadly consistent across tumor types following monotherapy and have not demonstrated clear dose-response or exposure-response relationships. Additionally, the simulated median and 95th prediction interval of nivolumab summary exposures across body weight range (35 - 160 kg) are predicted to be maintained below the corresponding observed highest exposure experienced in nivolumab ie, 95th percentile following nivolumab 10 mg/kg Q2W from clinical study CA209003. Thus, while subjects in the lower body weight ranges would have greater exposures than 80 kg subjects, the exposures are predicted to be within the range of observed exposures at doses (up to

10 mg/kg Q2W) used in the nivolumab clinical program, and are not considered to put subjects at increased risk. For subjects with greater body weights, the simulated ranges of exposures are also not expected to affect efficacy, because the exposures predicted following administration of a 240 mg Q2W are on the flat part of the exposure-response curves for previously investigated tumors, melanoma and NSCLC. Given the similarity of nivolumab PK across tumor types and the similar exposures predicted following administration of 240 mg flat dose compared to 3 mg/kg, it is expected that the safety and efficacy profile of 240 mg nivolumab will be similar to that of 3 mg/kg nivolumab. Thus nivolumab 240 mg every 2 weeks over 30 minutes for the first 4 months will be used this study.

At 4 months after initiation of treatment, subjects will be switched from nivolumab 240 mg every 2 weeks to nivolumab 480 mg every 4 weeks (Q4W), which provides a more convenient dosing regimen for subjects. Based on PK modeling and simulations, administration of nivolumab 480 mg Q4W will be started after steady state is achieved with 240 mg Q2W and is predicted to provide Cavgss similar to 240 mg Q2W. While 480 mg Q4W is predicted to provide greater (approximately 20%) maximum steady state concentrations and lower (approximately 10%) steady state trough concentrations, these exposures are predicted to be within the exposure ranges observed at doses up to 10 mg/kg Q2W used in the nivolumab clinical program, and are not considered to put subjects at increased risk. Similar to the nivolumab 240 mg Q2W dosing regimen, the exposures predicted following administration of nivolumab 480 mg Q4W, are on the flat part of the exposure-response curves for previously investigated tumors, melanoma and NSCLC, and are not predicted to affect efficacy. Based on these data, nivolumab 480 mg Q4W is expected to have similar efficacy and safety profiles to nivolumab 240 mg Q2W.

1.3.1.2 Rationale for Nivolumab 30 Minute Infusion

Long infusion times place a burden on subjects and treatment centers. Establishing that nivolumab can be safely administered using shorter infusion times of 30 minutes duration in subjects will diminish the burden provided no change in safety profile. Previous clinical studies show that nivolumab has been administered safely over 60 minutes at doses ranging up to 10 mg/kg over long treatment duration. In Study CA209010, (a Phase 2, randomized, double blinded, dose-ranging study of nivolumab in subjects with advanced/metastatic clear cell RCC) a dose association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg and 18.5% at 10 mg/kg). All the events were grade 1-2 and were manageable. An infusion duration of 30 minutes for 240 mg and 480 flat doses of nivolumab (~ 60% of the dose provided at 10 mg/kg) are not expected to present safety concerns compared to the prior experience at 10 mg/kg nivolumab dose infused over a 60 minute duration.

1.3.2 Rationale for Elotuzumab Development in Multiple Myeloma

Elotuzumab (BMS-901608, HuLuc63) is a first-in-class, immunostimulatory, humanized immunoglobulin G1 (IgG1) monoclonal antibody (mAb) targeted against Signaling Lymphocyte Activation Molecule Family 7 (SLAMF7, also called CS1), a glycoprotein highly expressed on myeloma cells independent of cytogenetic abnormalities. SLAMF7 is also expressed on natural killer (NK) cells and at lower levels on other immune cell subsets. SLAMF7 has not been detected

on hematopoietic stem cells, nor on other normal solid organ tissues. Elotuzumab binding to SLAMF7 directly activates NK cells, but not myeloma cells.[13,14] Elotuzumab bound to myeloma cells via SLAMF7 further activates NK cells via Fc receptors, thereby enabling selective killing of myeloma cells with minimal effects on normal tissue.[15]

Elotuzumab demonstrates a dual mechanism that includes: 1) direct NK cell activation and 2) NK cell-mediated Antigen Dependent Cellular Cytotoxicity (ADCC).

In a Phase 2 trial of elotuzumab combined with lenalidomide and dexamethasone for relapsed/refractory myeloma subjects, the objective response rate was 84% and median PFS was 29 months.[16]

Risks associated with elotuzumab in early phase studies appear to be limited primarily to infusion reactions. These infusion reactions are mitigated with the use of a standard regimen of histamine blocking agents, acetaminophen and corticosteroids. Investigator-determined infusion reactions were reported in 11% of subjects in the phase 2 trial.

Phase 3 Trial of Elotuzumab in relapsed/refractory MM

The study CA204004 is an ongoing Phase 3, randomized, open-label trial investigating the combination of elotuzumab with lenalidomide/low-dose dexamethasone (E-Ld) versus lenalidomide/low-dose dexamethasone alone (Ld) in subjects with previously treated relapsed or refractory multiple myeloma. The primary objectives of this study were to compare the ORR and PFS of E-Ld versus Ld. In total, 646 subjects were randomized and 635 were treated. At the time of the interim analysis data cut-off, 179 (elotuzumab group, 35%; control group 21%) were still on-treatment. The median follow up was 24.5 months and in the elotuzumab group, subjects received a median of 19 (range, 1 to 42) treatment cycles over a median of 17 months versus 14 (range, 1 to 40) over 12 months in the control group.

Hazard ratio for progression-free survival was 0.70 (95% confidence interval, 0.57 to 0.85; P=0.0004). 1-year progression-free survival rate in the elotuzumab group was 68%, versus 57% in the control group; 2-year rate was 41% versus 27%. Median progression-free survival in the elotuzumab group was 19.4 months versus 14.9 months in the control group. Overall response rate in the elotuzumab group was 79% versus 66% in the control group (P=0.0002).

In the 635 treated subjects, adverse events of any grade occurred in 99% of patients. In the elotuzumab group, 34% of the patients experienced grade 3 to 4 neutropenia versus 44% in the control group; 77% versus 49% of patients had grade 3 to 4 lymphopenia, respectively. The most common non-hematologic toxicities (> 30% of patients) included infections, fatigue, pyrexia, diarrhea, constipation, and cough. The most common grade 3 to 4 non-hematologic toxicities were fatigue and pneumonia. In the elotuzumab group, infections were reported for 81% of patients versus 74% in the control group. When adjusted for the longer drug exposure in the elotuzumab group, infection rates were equal in both groups (incidence rate per 100 patient years, 197). Consequently, despite the higher rate of lymphopenia observed in the elotuzumab group, there were no apparent untoward clinical manifestations.

In the elotuzumab group, study drug toxicity was the primary cause of death in 5 (2%) patients versus 6 (2%) in the control group.

Thirty-five (6%) patients had a second primary malignancy: 22 (7%) in the elotuzumab group and 13 (4%) in the control group. The incidence rates of second hematologic malignancies were identical in the elotuzumab and control groups (2% in each group); rates of second solid tumors were 3% versus 2%, respectively, and rates of non-melanoma skin cancers were 3.1% versus 1.5%, respectively. When adjusted for exposure to study therapy, the incidence rates of second primary malignancies per 100 patient-years were similar at 3.5 versus 2.8, respectively.

Thirty-three (10%) patients receiving elotuzumab had an infusion reaction, including pyrexia, chills, and hypertension. Infusion reactions were mostly grade 1 to 2; 1% were grade 3 reactions and none were grade 4 to 5. Most infusion reactions occurred in the first 2 cycles of study therapy (range cycle 1, day 1 to cycle 11, day 281); five patients had an infusion reaction after cycle 2. Infusion of elotuzumab was interrupted in 15 (5%) patients owing to an infusion reaction, for a median duration of 15 minutes. Infusion reactions resolved in all patients; however, 2 (1%) patients discontinued due to an infusion reaction.

Elotuzumab may be detected in the serum protein electrophoresis (SPEP) and serum immunofixation assays of myeloma patients and could interfere with correct response classification. A small peak in the early gamma region on SPEP that is IgGκ on serum immunofixation may potentially be attributed to elotuzumab, particularly in patients whose endogenous myeloma protein is IgA, IgM, IgD, or lambda light chain restricted. This interference can impact the determination of complete response and possibly relapse from complete response in patients with IgG kappa myeloma protein.

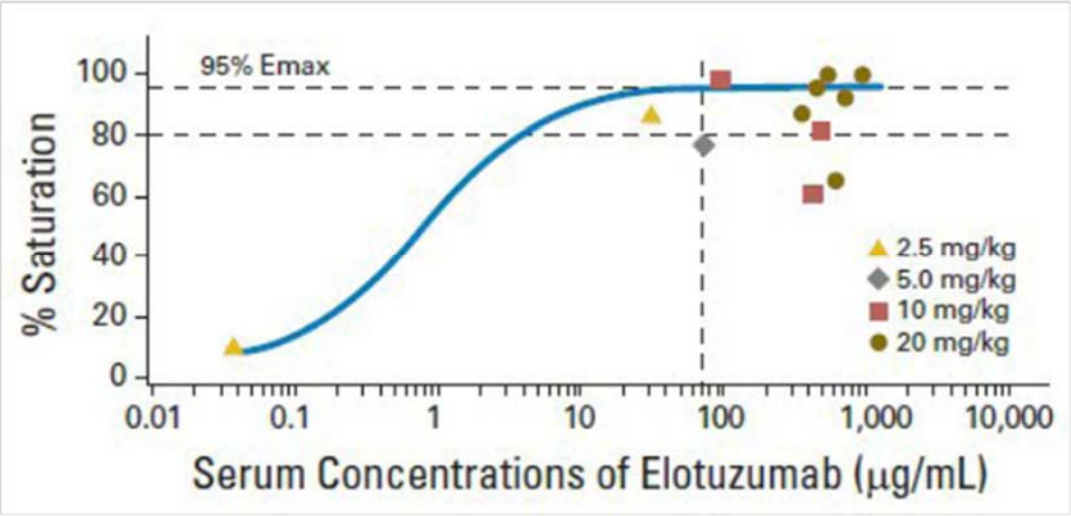
Elotuzumab was approved in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior therapies (FDA, November-2015) and in MM patients who have received at least one prior therapy (EMA, 2016). A description and status of all studies are presented in the Investigator Brochure.[17]

1.3.2.1 Rationale for Elotuzumab dose and frequency

The dose of 10 mg/kg on D1, 8, 15 & 22 of Cycles 1 and 2 then on D1 & 15 during Cycles 3 and 4, used in this protocol, is the FDA approved dose and regimen of elotuzumab in combination with lenalidomide and dexamethasone.

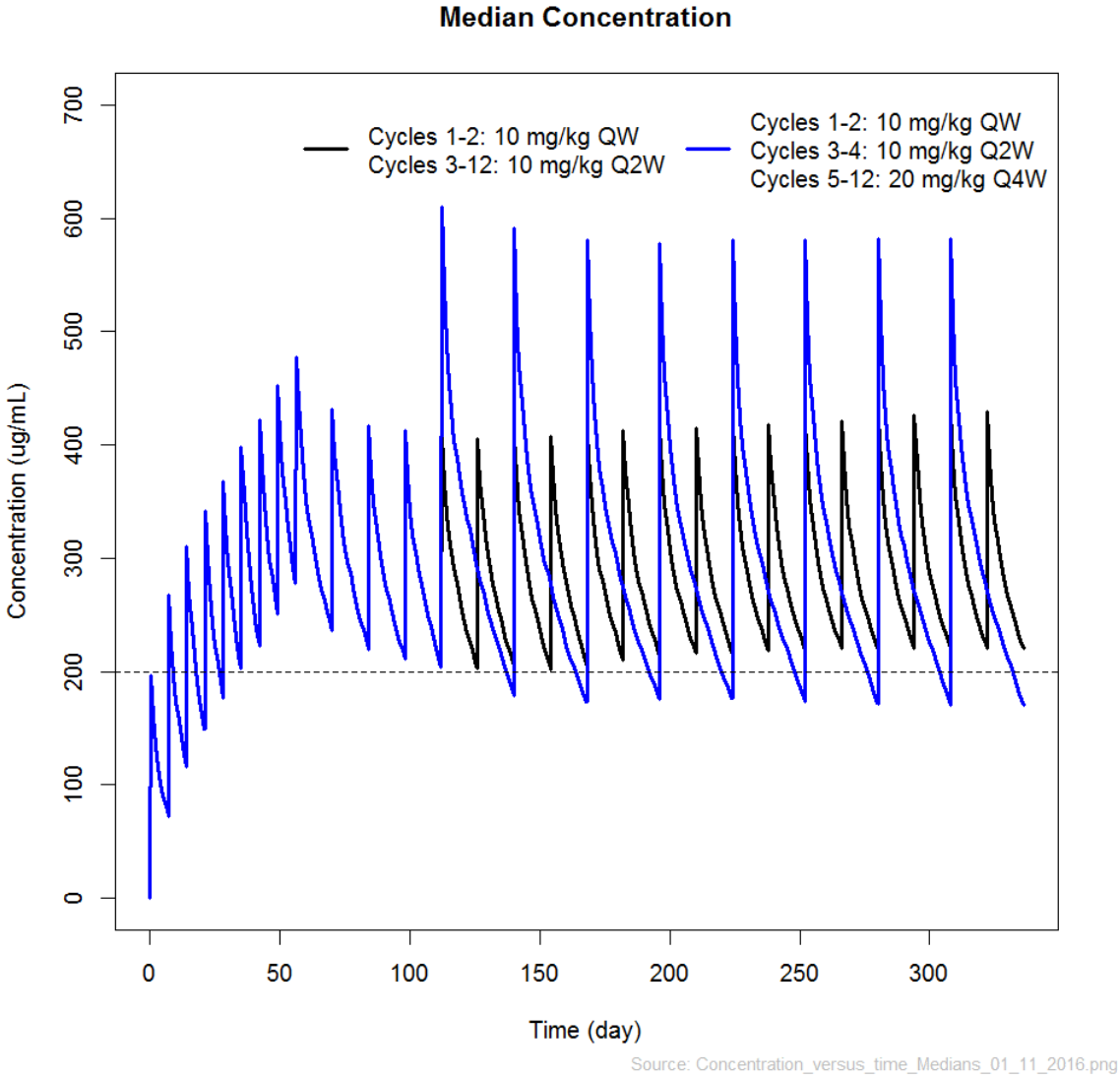
Clinical Phase I and IIa studies suggests that the trough serum concentrations of elotuzumab in subjects treated with 10 and 20 mg/kg doses are above the target levels ie, 70 µg/ml, which is predicted based on preclinical models. Following elotuzumab dosing of 10 and 20 mg/kg in combination with lenalidomide/dex, the observed steady-state Cmin values consistently remained above 70 µg/mL, the minimum efficacious trough concentrations[18]. Elotuzumab dosing also resulted in > 95% saturation of SLAMF7 on bone marrow plasma cells at doses ≥ 10 mg/kg (Figure 1.3.2.1-1).

Figure 1.3.2.1-1: Saturation of SLAMF7 Target on Bone Marrow Myeloma Samples from Subjects Treated in a Phase 2 Study of Elotuzumab and Lenalidomide/ Dexamethasone (HuLuc63 1703)



Beginning at Cycle 5, elotuzumab will be administered at 20 mg/kg once every 4 weeks. Increasing elotuzumab dose and decreasing the administration of elotuzumab frequency to every 4 weeks will continue to provide Cmin,ss above 70 ug/ml, and will be more convenient for patients on long term therapy and therefore require fewer scheduled clinic visits. With 20 mg/kg Q4W, the simulated Cave,ss is 301 ug/ml, which is similar to the 10mg/kg dosing regimen with Cave,ss value of 297 ug/ml. In addition, with the estimated Cmin,ss (geometric mean) is 141 ug/ml, and it remains above 70 ug/ml, which is the minimum trough concentration at which maximum efficacy was seen in preclinical studies and is sufficient to maintain saturation of SLAMF7 by elotuzumab. Further, with the 20 mg/kg Q4W dosing, the Cmax,ss (geometric mean) is estimated as 556 ug/ml, which is higher than the Cmax,ss of 401 ug/ml at the 10 mg/kg dose. However, in the PPK analysis of elotuzumab combination with len/dex, there was no relationship between elotuzumab exposure and Grade 3+ AEs hazard ratio. The point estimate indicated no increase in hazard ratio with increasing exposure over the range of exposures observed with a 10 mg/kg dosing regimen. This exposure-safety analysis indicates that increasing exposure may have limited impact on the safety for subjects.

Figure 1.3.2.1-2: Model of Elotuzumab Serum Concentration - 10 mg/kg of Study 004 and 20 mg/kg every 4 Weeks Starting Cycle 5



1.3.2.2 Elotuzumab Infusion Rate

The maximum infusion rate of 2 ml/min was initially explored in the phase 1 and 2 elotuzumab clinical trials. However, the infusion of elotuzumab at a faster rate was explored in 2 completed trials (HuLuc63-1703, CA204009) and 1 ongoing trial (CA204112). In the phase 2 portion of the HuLuc63-1703 trial, 31 subjects had the infusion rate escalated up to 5 mL/min (approximately 1 hour infusion). Of the total 3412 elotuzumab infusions administered, 1127 (33%) infusions were given at 5 mL/min. Nearly all the subject tolerated the faster infusion rate of elotuzumab without a reaction except 1 subject with a grade 1 event of nausea considered an infusion reaction by the investigator.

In the CA204009 trial, subjects in the E-Bd arm who did not have any infusion reaction in the first 4 cycles could have their infusion rate escalated to 5 ml/min. No infusion reactions were reported among the 41% of subjects and 19% of infusions administered at the faster rate of 5 ml/min.

In the CA204112 study, the infusion rate was escalated to 5mL/min starting C1D15. As of 13 Oct 2015, 70 subjects were treated with a median of 6 cycles (1 - 13). A total of 2 subjects (3%) experienced infusion reactions (pyrexia, grade 1, and infusion related reaction, grade 2). No grade 3 - 4 infusion reaction was reported. Of the total of 1113 elotuzumab infusions, 968 infusions were given at 5mL/min with no reported infusion reactions. The 2 infusion reactions observed were reported at the infusion rate of 2mL/min.

The 5 ml/min infusion rate for elotuzumab will be utilized in this trial based on its safety across several prior studies.

1.3.3 Rationale for Pomalidomide in Multiple Myeloma

Pomalidomide, a derivative of thalidomide with immunomodulatory properties, is approved as a treatment option for subjects with relapsed or refractory multiple myeloma who have received at least two prior therapies including lenalidomide and bortezomib and who have demonstrated disease progression on or within 60 days of completion of the last therapy.

Phase 3 Trial of Pomalidomide in Third Line

The phase 3 study (MM-003/NIMBUS® trial) evaluated the combination of pomalidomide with low-dose dexamethasone vs high-dose dexamethasone in refractory or relapsed and refractory MM subjects. A total of 302 patients were randomly assigned to receive pomalidomide plus low-dose dexamethasone and 153 high-dose dexamethasone.

Pomalidomide was dosed at 4 mg orally on Days 1-21 of each 28 day cycle and dexamethasone was given at a low dose of 40 mg/day on days 1, 8, 15, and 22, orally or at a high dose of 40 mg/day on days 1–4, 9–12, and 17–20, orally. Treatment continued until disease progression or unacceptable toxicity. The primary endpoint of the study was progression-free survival (PFS).

Efficacy data from this phase 3 study shows that median PFS with pomalidomide plus low-dose dexamethasone was 4.0 months (95% CI 3.6–4.7) versus 1.9 months (1.9–2.2) with high-dose dexamethasone (HR 0.48 [95% CI 0.39–0.60]; p<0.0001) favoring the pomalidomide plus low dose dexamethasone arm. The median overall survival was also significantly longer in the pomalidomide plus low-dose dexamethasone group than in the high dose dexamethasone group (12.7 months [95% CI 10.4–15.5] vs 8.1 months [6.9–10.8]; HR 0.74 [0.56–0.97]; p=0.0285). Overall response rate after a median follow-up of 10.0 months was documented in 31% of 302 patients in the pomalidomide plus low-dose dexamethasone group versus 10% of 153 in the high-dose dexamethasone group (odds ratio [OR] 4.22 [2.35–7.58]; p<0.0001).

Regarding safety, the most common grade 3–4 hematological adverse events in the pomalidomide plus low dose dexamethasone and high-dose dexamethasone groups were neutropenia (48% vs 16% respectively), anaemia (33% vs 37%), and thrombocytopenia (22% vs 26%). Grade 3–4 non-hematological adverse events in the pomalidomide plus low-dose dexamethasone and

high-dose dexamethasone groups included pneumonia (13% vs 8%), bone pain (7% vs 5%), and fatigue (5% vs 6%).

The dose of pomalidomide in this study will be 4 mg orally on Days 1-21 of each 28 day cycle in combination with low dose dexamethasone (40 mg/day on days 1, 8, 15, and 22, orally for patients ≤75 years old, and 20 mg/day on days 1, 8, 15, and 22, orally for patients >75 years old) which is the approved dose and schedule for treatment of this population.

1.3.4 Rationale for combining Nivolumab and Pomalidomide in Multiple Myeloma

The exact mechanism(s) needed to sensitize BM T cells from MM patients to PD-1 blockade is unknown but in part may require a reversal of T cell senescence that has been observed in MM[19]. In fact, one report presents data supporting the capacity of low concentrations of lenalidomide to improve several of the T cell abnormalities of immunosenescence, suggesting it may be a beneficial therapy for restoration of T cell-dependent immunity, especially in the elderly which is the target demographic for most patients with MM. However, this observation has not been validated with T cells from the phenotypes ascribed above to MM patients.[19] Therefore, in addition to the MoAs described for PD-1/PD-L1 blockade and IMiDs in restoring immune surveillance, perhaps IMiDs may also contribute to the reversal of T cell senescence and may at least partially sensitize these compromised T cells to PD-1 blockade.

Due to the overlap in rationale for blocking PD-1 versus blocking PD-L1, most of the pre-clinical data supports that both approaches generate similar results with regards to enhancing T and NK cell function and enhancing the killing of myeloma cells. However, there are some subtle yet distinct differences between these two approaches (Figure 1.3.4-1). Blocking PD-1 inhibits both PD-1: PD-L1 and PD-1: PD-L2 interactions. Antibodies directed toward PD-L1 would block interactions with PD-1 but would not impair PD-L2 interactions with PD-1.

Figure 1.3.4-1: Interactions of B7 ligand family members to CD28 receptor family members

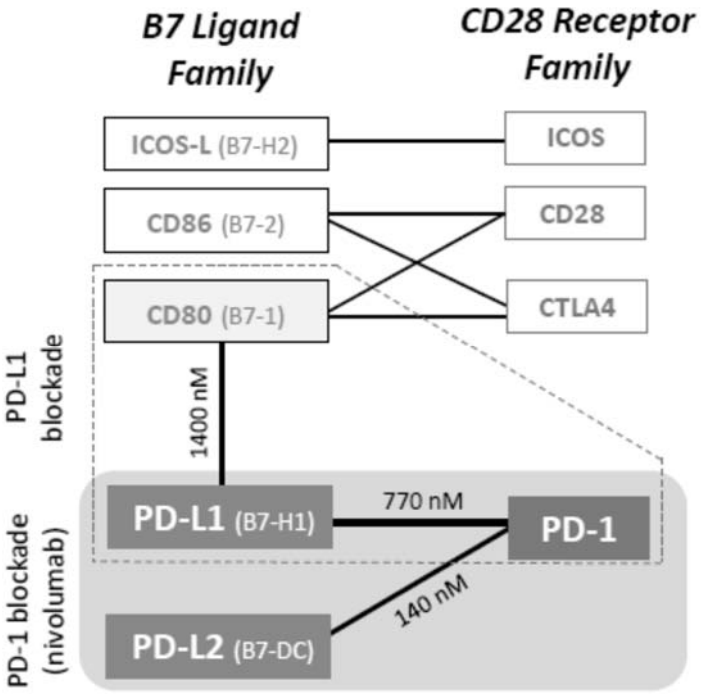


Figure 1.3.4-2 summarizes the current understanding of the potential mechanisms for combining an IMiD with a PD-1 (or PD-L1) blocking antibody and how these effects would shift the balance to restoring immune surveillance in MM.

Figure 1.3.4-2: Interactions of B7 ligand family members to CD28 receptor family members

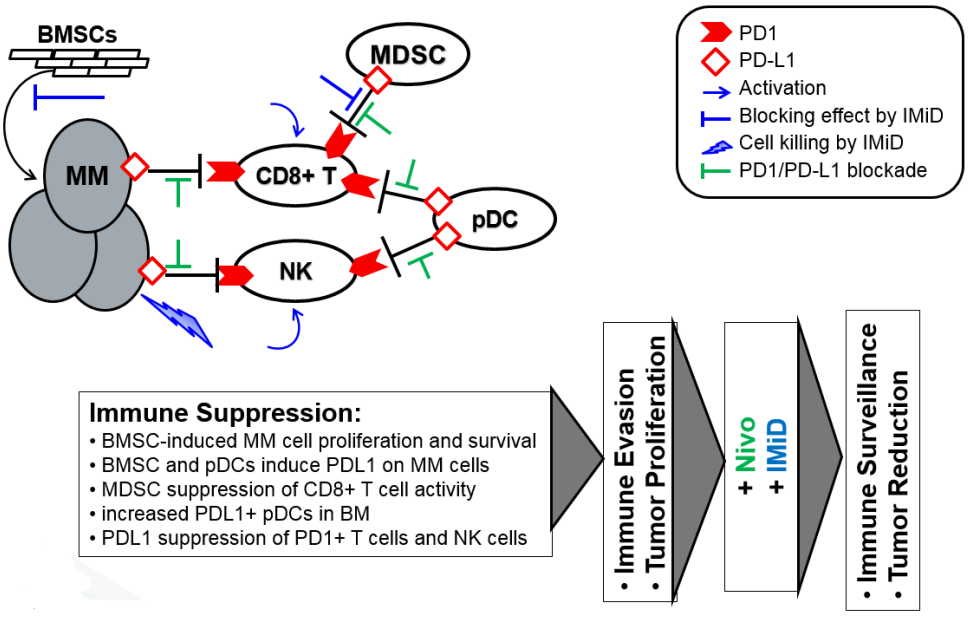


Figure 1.3.4-2: Proposed model representing the combination effects of IMiDs and blocking antibodies to the PD-1/PD-L1 axis.

Phase 2 Trial of PD-1 Inhibitor with Pomalidomide in 3rd Line Myeloma

An ongoing phase 2 study single arm is evaluating the safety and efficacy of a similar PD-1 inhibitor (pembrolizumab) in combination with pomalidomide and low dose dexamethasone in relapsed/refractory multiple myeloma patients.

Of the first 24 patients, 75% had prior autologous transplantation and 96% were refractory to last therapy. All patients had received both IMiDs and Proteosome inhibitors; 75% were double refractory to both IMiDs and Proteosome inhibitors and additional 21% were refractory to lenalidomide alone. Patients had received a median of 3 lines of prior therapy (range: 1-6). The median time from MM diagnosis to study entry was 4 years (range: 1.2-15).

Preliminary safety and efficacy data for the first 24 subjects demonstrated no infusion-related reactions. Hematologic toxicities (≥ grade 3) were neutropenia (29%), lymphopenia (17%) and thrombocytopenia (8%). Non-hematologic adverse events included (Grade ≤ 2; ≤ 3): fatigue (n=12; 1), constipation (n=10; 0), dyspnea (n=9; 2), itching (n=6; 0), muscle spasms (n=6; 0), infection (n=4; 3), hyperglycemia (n=5; 0), edema (n= 4; 0), fever (n=3; 0), palpitation (n=2; 1), rash (n=3; 1) and hypotension (n=3; 0). Events of clinical significance, autoimmune mediated, included hypothyroidism (n=2), transaminitis (n=2), and pneumonitis (n=1). Four patients had pomalidomide dose reductions due to rash, neutropenia, palpitations and fatigue. Two patients died; one after cycle 1 (progressive disease) and one during cycle 2 (sepsis). Objective responses (modified IMWG criteria) were observed in 11 of 22 evaluable patients (50%) including: near complete response (n=3), very good partial response (n=2), partial response (n=6); additionally, 3 patients had minimal response, 6 had stable disease and 2 progressed. At a median follow up of 16 weeks; 17 of 22 patients continued on the study.

Phase 1 Trial of PD-1 Inhibitor with Lenalidomide in Myeloma

Another ongoing phase 1 study combining the PD1 inhibitor pembrolizumab with lenalidomide and dexamethasone in patients with relapsed/refractory multiple myeloma has demonstrated a tolerable safety profile of the PD1 inhibitor and IMiD combination. Among the first 17 evaluable subjects, sixteen (94%) experienced at least 1 adverse event (AE) of any grade related to study treatment and 10 (58%) experienced grade 3/4 treatment-related AEs. No death or treatment discontinuation for toxicity has been observed. The most frequent treatment-related AEs were: thrombocytopenia (47%), neutropenia (41%), fatigue (29%), and anemia, hyperglycemia, and muscle spasms (23% each). No DLTs were observed in the 10-mg lenalidomide cohort. In the 25-mg lenalidomide cohort, 3 patients (3/13) experienced a dose-limiting toxicity (DLT): neutropenia (grade 3 and grade 4), infectious pneumonia (grade 3), and tumor lysis syndrome (grade 3) with hyperuricemia (grade 4). All patients recovered from the DLTs without treatment discontinuation. Based upon these data the MTD/MAD was defined as pembrolizumab 200 mg fixed dose in combination with lenalidomide 25 mg and low-dose dexamethasone 40 mg. The preliminary efficacy was also promising in this study with 76% ORR reported so far.

1.3.5 Rationale for combining Elotuzumab and Pomalidomide in Multiple Myeloma

Combining elotuzumab with lenalidomide, a thalidomide analog with immunomodulatory properties, is well tolerated and was proven to result a statistically and clinically meaningful improvement over lenalidomide/dexamethasone alone in a phase 3 trial.

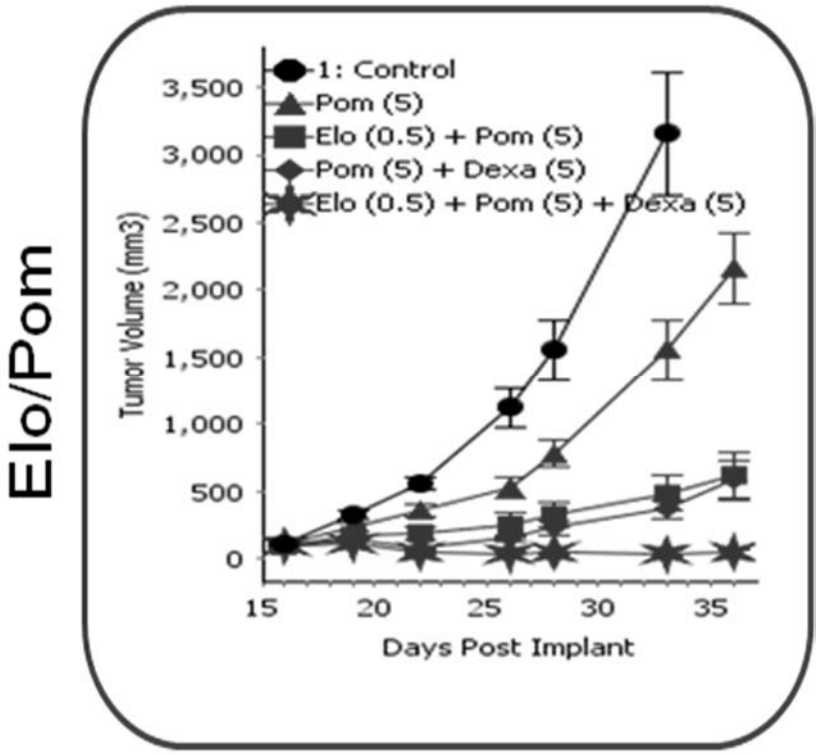
Pomalidomide, in the same class as lenalidomide, is approved as a treatment option for subjects with relapsed or refractory multiple myeloma who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy.

In in vitro cellular assays, pomalidomide inhibited proliferation and induced apoptosis of hematopoietic tumor cells. Additionally, pomalidomide inhibited the proliferation of lenalidomide-resistant multiple myeloma cell lines and synergized with dexamethasone in both lenalidomide-sensitive and lenalidomide-resistant cell lines to induce tumor cell apoptosis. Pomalidomide enhanced T cell- and natural killer (NK) cell-mediated immunity and inhibited production of pro-inflammatory cytokines (eg, TNF-α and IL-6) by monocytes[20].

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 antibody-dependent cell-mediated cytotoxicity (ADCC) towards primary myeloma cells in a similar way to that observed with lenalidomide.

Figure 1.3.5-1 illustrates results from pre-clinical data (Robbins et al, unpublished) showing the combination of elotuzumab with pomalidomide +/- dexamethasone (SCID-ICR mice with OPM2 xenograft) is similar to the combination of elotuzumab and lenalidomide that has been previously reported[21]. Therefore, in pre-clinical models of MM, the combination of elotuzumab/pomalidomide enhances the killing of SLAMF7+ myeloma cells in vivo greater than either agent alone. Additionally, low doses of dexamethasone do not appear to impair NK function in this model and adds to the anti-myeloma activity of the combination in this model.

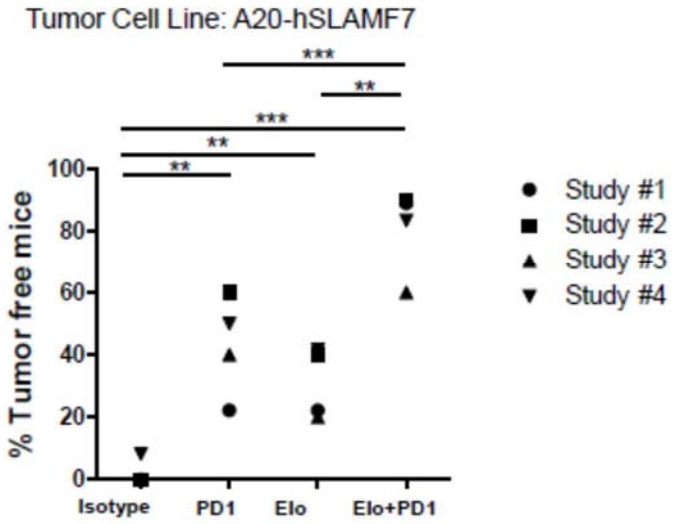
Figure 1.3.5-1: Elotuzumab Synergizes with Pomalidomide to Kill SLAMF7+ Human MM Cells in vivo



1.3.6 Rationale for combining Elotuzumab and Nivolumab in Multiple Myeloma

It has been previously shown in pre-clinical models that elotuzumab activity towards MM cells can be improved by agents that enhance NK cell activity, either through agonizing activating molecules or blocking inhibitory molecules on the surface of NK cells[22]. Consistent with this rationale, PD-1 expression has been shown on both T cells and NK cells in bone marrow samples from MM patients, therefore blocking the PD-1/PD-L1 axis may also contribute to increased elotuzumab activity towards killing myeloma cells. Figure 1.3.6-1 shows that in pre-clinical in vivo models, the combination of elotuzumab and a murine surrogate antibody of nivolumab demonstrates enhanced reduction of tumors in mice.[23] These results were generated in a completely immune competent syngeneic mouse tumor model therefore the net anti-tumor activity observed can be mediated by both innate (NK) and adaptive (T cell) immunity.

Figure 1.3.6-1: Elotuzumab Synergizes with a PD-1 blocking antibody to Kill SLAMF7+ Tumor Cells in vivo



1.4 Research Hypothesis

The addition of nivolumab to pomalidomide and dexamethasone will increase the clinical benefit represented by increased progression free survival (PFS) and higher response rate compared to pomalidomide and dexamethasone in subjects with relapsed and/or refractory multiple myeloma.

1.5 Objectives(s)

1.5.1 Primary Objectives

The primary objective is to compare progression free survival (PFS) between N-Pd and Pd arms, by investigator.

1.5.2 Secondary Objectives

- To estimate overall survival (OS) within N-Pd and Pd arms
- To assess the time to objective response (TTR) within N-Pd and Pd arms by investigator.
- To assess the duration of objective response (DOR) within N-Pd and Pd arms by investigator.
- The compare objective response rate (ORR) between N-Pd and Pd arms, by investigator.

1.5.3 Exploratory Objectives

- To evaluate efficacy of NE-Pd in subjects with relapsed and/or refractory multiple Myeloma within NE-Pd arm through the assessment of ORR and PFS
- To evaluate efficacy of NE-Pd in subjects who crossed-over from the control arm (Pd) to the exploratory arm (NE-Pd) through the assessment of ORR and PFS
- To assess safety and tolerability

[redacted]

[redacted]

1.6 Product Development Background

1.6.1 Clinical Summary

1.6.1.1 Summary of Nivolumab Clinical Pharmacokinetics

The pharmacokinetics (PK) of nivolumab were studied in subjects over a dose range of 0.1 to 10 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. The geometric mean (% CV%) clearance (CL) was 9.5 mL/h (49.7%), geometric mean volume of distribution at steady state (Vss) was 8.0 L (30.4%), and geometric mean elimination half-life (t1/2) was 26.7 days (101%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg Q2W, and systemic accumulation was approximately 3-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. The clearance of nivolumab increased with increasing body weight. The PPK analysis suggested that the following factors had no clinically important effect on the CL of nivolumab: age (29 to 87 years), gender, race, baseline LDH, PD-L1. A PPK analysis suggested no difference in CL of nivolumab based on age, gender, race, tumor type, baseline tumor size, and hepatic impairment.

Although ECOG status, baseline glomerular filtration rate (GFR), albumin and body weight had an effect on nivolumab CL, the effect was not clinically meaningful. Additionally, PPK and exposure response analyses have been performed to support use of 240 mg Q2W dosing in addition to the 3 mg/kg Q2W regimen. Using the PPK model, exposure of nivolumab at 240 mg flat dose was identical to a dose of 3 mg/kg for subjects weighing 80 kg, which was the approximate median body weight in nivolumab clinical trials (see Section 1.3.1.1).

Full details on the clinical pharmacology aspects of nivolumab can be found in the Investigator Brochure.

1.6.1.2 Summary of Relevant Clinical Data

Nivolumab Phase 1 Monotherapy Results in hematological malignancies including Myeloma

Preliminary safety data from an ongoing Phase 1 study for patients with a variety of hematologic malignancies (CA209039) suggested that the safety for these malignancies seems similar to that for solid tumors. As of 02-May-2015, data were available for 105 patients, including 27 subjects with MM, treated with Nivolumab monotherapy. Treatment with nivolumab in patients with hematological malignancies has been well tolerated and toxicities have been generally manageable. There was 1 DLT (Dose Limiting Toxicity) at the 1 mg/kg dose level in a patient

with multiple myeloma who experienced Grade 3 pneumonia and Grade 3 pneumonitis. There was 1 DLT at the 3 mg/kg dose level in a patient with small lymphocytic lymphoma who experienced Grade 3 hypereosinophilia and Grade 3 diplopia. The MTD was not reached.

Adverse events were reported in 104 of 105 (99%) patients and Grade ≥ 3 events in 64 (61%) patients. Related AEs were reported in 72 (68.6%) patients. Those that occurred in more than 5% of patients included: fatigue (16.2%), rash (10.5%), pneumonitis (9.5%), pruritus (9.5%), diarrhea (8.6%), pyrexia (8.6%), decreased appetite (7.6%), thrombocytopenia (6.7%), leukopenia (5.7%), lymphopenia (5.7%), hypocalcaemia (5.7%) and lipase increased (5.7%). Related Grade ≥ 3 events were reported in 23 (21.9%) patients; the most common of which was leukopenia that occurred in 4 (3.8%) patients. twenty five (23.8%) patients discontinued therapy due to AEs, 15 of which were related to study therapy. A total of 37 (35.2%) patients died: 28 due to disease, 8 due to other causes, and 1 due to drug toxicity. Drug-related pneumonitis was observed in 10 patients (9.5%): Seven patients had Grade 1 or 2 pneumonitis; 2 had Grade 3; one patient had Grade 4.

Preliminary efficacy results in 27 relapsed/refractory multiple myeloma patients have demonstrated stable disease among 63% of patients with the remainder progression on single agent nivolumab.

1.7 Overall Risk/Benefit Assessment

Multiple myeloma (MM) is the second most prevalent blood cancer after non-Hodgkin lymphoma, representing 10% of hematologic malignancies. 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[24]. The subjects treated in this trial will receive an anti-myeloma regimen of pomalidomide + dexamethasone which demonstrated improvements in PFS, overall survival, and overall response in patients with refractory or relapsed and refractory multiple myeloma, including patients with disease refractory to both bortezomib and lenalidomide[25].

Pomalidomide has gained U.S. FDA and EMA approval in this population of MM patients at a dose of 4 mg, which is the dose being used in this trial. 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. Subjects must follow the local commercial Pomalidomide Pregnancy Risk Prevention Plan. For those countries where local Pomalidomide Pregnancy Prevention Program does not exist, subjects must follow the Pomalidomide Global Pregnancy Prevention Plan for clinical trials (Appendix 6). All investigators and subjects must fully comply with and participate in the pregnancy prevention program in order to participate in this trial.

Nivolumab is approved in multiple solid tumor indications 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 5.

Emerging preliminary data on safety and efficacy of the PD1 inhibitor pembrolizumab in combination with IMiDs (pomalidomide and lenalidomide) in relapsed/refractory multiple myeloma patients have demonstrated a clinical benefit and was well tolerated. Being a PD1 inhibitor, nivolumab is expected to have an acceptable tolerance profile in combination with pomalidomide similar to that of pembrolizumab.

Elotuzumab has proven activity in relapsed/refractory multiple myeloma patients in combination with IMiDs. The addition of elotuzumab to lenalidomide and low dose dexamethasone has significantly prolonged the PFS compared to lenalidomide and low dose dexamethasone.

Elotuzumab as monotherapy or in combination with immunomodulatory agents such as thalidomide or lenalidomide is well tolerated. Safety data from 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). Key elotuzumab adverse events have been infusion related events[26]. 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.

Since lenalidomide and pomalidomide are in the same class of drugs, and have a similar safety and pharmacokinetic profile, elotuzumab is expected to elicit a similar safety profile in combination with pomalidomide as it did in the lenalidomide - elotuzumab and thalidomide -elotuzumab combinations.

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

Based on the above assessment, the potential benefit of combining nivolumab and elotuzumab with pomalidomide and dexamethasone appears to outweigh the potential risk. The overall risk/benefit assessment supports the evaluation of these combinations in this setting.

It is possible that unforeseen or unanticipated adverse events may occur. 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. Additionally, to ensure subjects' safety, an independent Data Monitoring Committee (DMC) will also be established to monitor the

safety of subjects treated with the combination regimens regularly and identify any early safety signal.

Recent safety concerns of increased risk of mortality and severe adverse events have been reported from two studies with pembrolizumab, an anti-PD-1 monoclonal antibody not approved for treatment of multiple myeloma, in combination with IMiD (lenalidomide and pomalidomide) and dexamethasone (https://www.fda.gov/Drugs/DrugSafety/ucm574305.htm). In light of these safety concerns, on 1 September 2017 the FDA requested that CA209602 be placed on partial clinical hold. As a consequence, as of 1-September-2017, enrollment in this study was stopped, as well as the cross-over of subjects randomized to the Pd control arm into the exploratory NE-Pd arm. Subjects on treatment as of 1-September-2017 who were deriving clinical benefit can continue treatment and must be monitored as per protocol requirements. As of Revised Protocol 02, the exploratory NE-Pd arm is removed from the study design, and enrollment in the study is focused on the investigational (N-Pd) and control (Pd) arms.

At FDA request, an interim PFS futility analysis based on the 12- April- 2018 database lock was performed to compare PFS between NPd and Pd arms. Based on the results of this futility analysis, on 23-August-2018 Bristol-Myers Squibb (BMS) has decided to permanently discontinue enrollment into the study due to insufficient evidence. The number of deaths that have occurred in the Arm NEPd (50%) were higher compared to those in the Arm NPd (29%) and Arm Pd (23%).

Three additional subjects in Arm Pd who crossed over to Arm NE-Pd have died due to disease progression, resulting in a total of 19 (27%) deaths in Arm Pd.

Among all treated subjects, the rates of serious adverse events [SAE] were higher in patients in Arm N-Pd (58%) and Arm NE-Pd (63%) compared to patients in Arm Pd (50%).

Deaths were mostly due to disease progression. Non-progression related causes of death are variable, with no distinct pattern or unifying mechanism. One death due to study drug toxicity was observed on the NPd arm due to pneumonitis complicated by pneumocystis infection.

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
3) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study
4) 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
5) 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
6) 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
7) 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 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 3 multicenter, randomized, open label study designed to evaluate the clinical benefit and safety of the combination therapy of Nivolumab, pomalidomide, and dexamethasone (N-Pd the investigational arm A), when compared to pomalidomide and dexamethasone (Pd; the control arm B) in subjects with relapsed and/or refractory multiple myeloma (rrMM).

Up to Revised Protocol 01, the study design included an exploratory third arm evaluating the clinical benefit and the safety of the combination therapy of elotuzumab, nivolumab, pomalidomide and dexamethasone (NE-Pd, the exploratory arm-[arm C]) in the same patient population. Additionally, subjects randomized to the Pd arm were allowed to cross over to this exploratory NE-Pd arm at the time of progression. Cross over was stopped as of 1 September 2017.

Enrollment in the NE-Pd exploratory arm was stopped as of Revised Protocol 02. All subjects already randomized to the NE-Pd arm, or who crossed over from the Pd to the NE-Pd arm will continue on study as long as they have clinical benefit and do not meet the study discontinuation criteria.

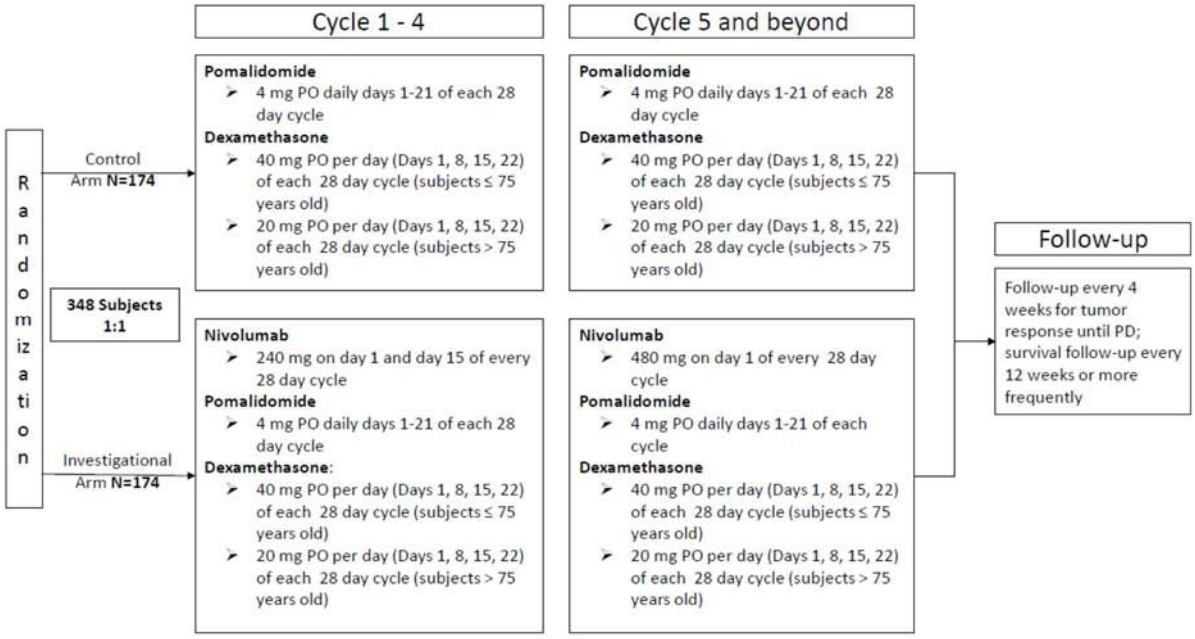
Initially, the study was designed to enroll approximately 417 subjects for a total of 348 subjects to be randomized (assuming 20% screen failure rate) to N-Pd and Pd arms in a 1:1 ratio. Randomization was performed with the following stratification factors: a) number of lines of prior therapy (2 vs 3+); AND b) ISS stage (1-2 vs 3).

Subjects were to continue treatment as long as the subject has clinical benefit from the treatment and does not meet criteria for treatment discontinuation.

As of 23-August-2018, any additional enrollment of CA209602 study was permanently closed due to the insufficient benefit observed based on the interim futility analysis of PFS. A total of 170 subjects were randomized into the study: 75 to NPd, 71 to Pd and 24 to NE-Pd arms. Subjects randomized to the NPd or NEPd arms may continue treatment based on investigator's judgement of continued clinical benefit. Study will be closed after all subjects complete safety follow-up (i.e., 100 days after the last subject has discontinued study treatment).

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 will be 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) Must have received ≥ 2 prior lines of therapy which must have included an immune modulatory drug (IMiD) and a proteasome inhibitor (PI) alone or in combination. Subject must have received at least 2 consecutive cycles of an IMiD and at least 2 consecutive cycles of a PI. The dose of the prior IMiD (eg lenalidomide) to which the subject has relapsed or been refractory must be the induction dose and NOT a maintenance dose (Note: adjusted induction dose for intolerance reasons or for renal impairment is accepted).

b) Documented refractory or relapsed and refractory (R/R) multiple myeloma

c) Refractory (lack of response or progressed on or within 60 days of the last dose of treatment) to their last line of treatment. Lack of response is defined as not having achieved at least PR. (Rajkumar et al., Blood 2011)[27]

d) Subjects must have failed treatment with a proteasome inhibitor and an IMiD (alone or in combination) in one of the following ways[27]

i) "Refractory" = Refractory (lack of response or progressed on treatment or within 60 days of the last dose of treatment, regardless of the achievement of initial response) to a proteasome inhibitor and an IMiD (alone or in combination). Lack of response is defined as not having achieved at least PR. (Rajkumar et al., Blood 2011)[27]

ii) "Relapsed and refractory"= Relapsed and refractory (achieve at least a partial response) to previous treatment with proteasome inhibitor or IMiD (alone or in combination) but then progressed after 60 days of the last dose of treatment.

e) Measurable disease at screening, based on central lab results within 28 days of randomization, defined as one or more of the following:

i) Serum IgG, IgA, or IgM M-protein ≥ 0.5 g/dL (5 g/L)

ii) Urine M-Protein ≥ 200 mg (0.2 g) excreted in a 24-hour collection sample

iii) Involved serum free light chain (sFLC) ≥ 100 mg/L (10 mg/dL) provided the FLC ratio is abnormal

f) Eastern Cooperative Oncology Group (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, subject has not been randomized / has not been treated). If re-enrolled, the subject must be re-consented

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 two negative serum or urine pregnancy tests (minimum sensitivity 25 mIU/mL or equivalent units of HCG). One 10-14 days prior to start of the study drug and one within 24 hours prior to the start of study drug

   i) WOCBP must agree to follow instructions for method(s) of contraception from the time of enrollment for the duration of treatment with study drug plus 5 half-lives of study drug plus 30 days (duration of ovulatory cycle) for a total of 23 weeks (except the Pd arm- where only 4 weeks is required) post treatment completion

   ii) Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 5 half-lives of study drug plus 90 days (duration of sperm turnover) for a total of 31 weeks (except the Pd arm -where only 4 weeks is required) post-treatment completion

c) Women must not be breastfeeding

d) Male patients must not donate sperm, for up to 7 months (4 weeks only for Pd arm) post treatment completion

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

f) All subjects must not donate blood for 90 days post treatment completion

g) All subjects must be willing and able to comply with Pomalyst® REMS program, where applicable

h) All subjects must agree not to share study medication

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.

At a minimum, subjects must agree to the use of two methods of contraception, with one method being highly effective and the other method being either highly effective or less effective as listed in the informed consent document.

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Subjects with solitary bone or extramedullary plasmacytoma as the only evidence of plasma cell dyscrasia

b) Subjects with monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM), primary amyloidosis (without 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)

2. Medical History and Concurrent Diseases

a) Women who are of childbearing potential not complying to the above described contraceptive measures or are breastfeeding, and sexually active fertile men whose partners are WOCBP if they are not complying to the above described contraceptive measures

b) Any uncontrolled or severe cardiovascular or pulmonary disease determined by the investigator, including:

i) NYHA functional classification III or IV, congestive heart failure, unstable or poorly controlled angina, uncontrolled hypertension, serious arrhythmia, or myocardial infarction in the past 12 months

ii) Subjects with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity

c) Active systemic infection

d) 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

e) 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

f) Unable to tolerate thromboembolic prophylaxis while on the study

g) Serious hypersensitivity reaction (as per investigator assessment) to prior IMiD (thalidomide or lenalidomide)

h) Grade ≥ 2 peripheral neuropathy (per NCI CTCAE v4.0)

i) Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic infection

j) Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at sites where mandated by local regulation

k) Gastrointestinal disease that may significantly alter the absorption of pomalidomide

l) Prior or concurrent invasive malignancy, except for the following:

i) Adequately treated basal cell or squamous cell skin cancer

ii) Adequately treated in-situ cancer

iii) Any cancer (other than those noted above) from which the subject has been disease free for > 3 years prior to study entry

3. Prior Therapy or Surgery

a) Prior treatment with pomalidomide or nivolumab (or any PD-1 or PD-L1 inhibitor).

b) 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

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

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

e) 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

f) 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

g) 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

h) Treatment with plasmapheresis within 4 weeks prior to randomization.

i) Subjects who have received a live / attenuated vaccine within 30 days of first treatment.

4. Physical and Laboratory Test Findings

Screening Laboratory evaluations within the following parameters:

a) Absolute neutrophil count (ANC) < 1,000 cells/μL (1.0 x 10^9/L) (Growth factors cannot be used within 1 week of first drug administration. No pegylated growth factors within 3 weeks of first drug administration)

b) Platelet count < 75,000 cells/μL (75 x 10^9/L) (< 30 x 10^9/L if ≥ 50% of bone marrow nucleated cells were plasma cells). Qualifying laboratory value must occur at most recent measurement prior to study entry. No transfusions are allowed within 72 hours prior to qualifying laboratory value

c) Hemoglobin < 8 g/dl (No transfusions are allowed within 72 hours prior to qualifying laboratory value)

d) Total Bilirubin > 1.5 X upper limit of normal (ULN) (except subjects with Gilbert Syndrome, who can have total bilirubin up to 3.0 X ULN)

e) AST (SGOT) and ALT (SGPT) > 3.0x ULN

f) Renal function: Estimated creatinine clearance by Cockcroft-Gault formula < 30 mL/min

- Female CrCl = (140 - age in years) x weight in kg x 0.85

  72 x serum creatinine in mg/dl

- Male CrCl = (140 - age in years) x weight in kg x 1.00

  72 x serum creatinine in mg/dl

g) Corrected serum calcium ≥ 11.5 mg/dl within 2 weeks of initiation of study drug (despite appropriate measures such a short course of steroids, bisphosphonates, hydration, calcitonin)

5. Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to study drug components

b) History of severe hypersensitivity reaction to any monoclonal antibody

6. Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated. (Note: under certain specific circumstances a person who has been imprisoned may be included or permitted to continue as a subject. Strict conditions apply and Bristol-Myers Squibb approval is required

b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

3.3.3 Women of Childbearing Potential

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 > 40 mIU/mL to confirm menopause.

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

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

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

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

Any systemic, anti-myeloma therapy other than the study drugs is prohibited while on study therapy. Concomitant steroids, other than weekly dexamethasone or steroids allowed (as defined in eligibility criteria) are prohibited unless used to treat an adverse event. Guidelines for selection and use of other concomitant medications should be derived from the pomalidomide and dexamethasone prescribing information.

Avoid co-administration of pomalidomide with strong inhibitors of CYP1A2 unless medically necessary. Co-administration of pomalidomide with drugs that are strong inhibitors of CYP1A2 (eg, ciprofloxacin, enoxacin and fluvoxamine) and CYP3A4/5 (eg, ketoconazole) or P-gp could increase pomalidomide exposure and should be avoided, unless medically necessary[28, 29]. The FDA DDI database link is the following:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

Other than study medications, administration of any therapeutic or diagnostic investigational agent (for any indication) is prohibited while on study therapy without prior Sponsor approval.

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

Any live / attenuated vaccine (eg varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella (MMR)) is prohibited during treatment and until 100 days post last dose.

3.4.2 Required Treatment

Subjects must receive thrombo-embolic prophylaxis, per institutional guidelines or PI discretion. Examples of commonly used thrombo-embolic prophylaxis medications include aspirin, low molecular weight heparin, and vitamin K antagonists.

Subjects must receive pre-medications (Sections 4.5.1.3.6 and 4.5.1.3.7) prior to each dose of elotuzumab.

3.4.3 Permitted at Investigator's Discretion

IV corticosteroids, diphenhydramine, or hydroxyzine, acetaminophen/ paracetamol, H2 inhibitors (ie, cimetidine), leukotriene inhibitors (montelukast sodium) for the management of infusion reactions. Additional supportive measures should be provided as indicated including:

- oxygen inhalation
- epinephrine
- bronchodilators
- oral antiviral and antimicrobial prophylaxis

- anti-emetics
- bisphosphonates

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

Per the ASCO 2007 Clinical Practice Guidelines[30], bisphosphonate therapy should be administered for a period of 2 years. At 2 years, the investigator should seriously consider discontinuing bisphosphonates in subjects with at least stable disease, although further use is at the discretion of the investigator.

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

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

3.4.4 Surgery and Radiation

Use of radiotherapy or surgical intervention must be recorded on the appropriate Case Report Form.

Localized radiation therapy to a site of pre-existing disease may be permitted while on study. Following approval by the medical monitor, the subject may continue with protocol therapy without interruption during the course of palliative radiation therapy if the investigator believes that the risk of excessive bone marrow suppression or other toxicity is acceptable, and it is in the best interest of the subject to do so.

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

Kyphoplasty, vertebroplasty, or emergency orthopedic surgery is permitted.

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
- Progressive Disease according to IMWG criteria
- 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)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Subjects who receive any non-protocol specified systemic anti-myeloma therapy before documented progression will be discontinued from all study treatment (including pomalidomide and 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 only. Subjects may continue nivolumab, pomalidomide and dexamethasone treatment. Refer to Section 4.5.4.
- Subjects experiencing angioedema, Grade 4 rash, exfoliative or bullous rash, Stevens Johnson syndrome, or toxic epidermal necrolysis must discontinue pomalidomide and nivolumab. Subjects may continue on elotuzumab and dexamethasone.
- Subjects experiencing a 56 day delay in all study drugs (nivolumab, pomalidomide, dexamethasone, and elotuzumab) 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 BMS Medical Monitor.
- Subjects experiencing a Grade 3 or 4 infusion reaction related to nivolumab must discontinue nivolumab only. Subjects may continue elotuzumab, pomalidomide and dexamethasone treatment. Refer to Section 4.5.4 for additional reasons to discontinue nivolumab dosing permanently.

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 patient chose to terminate the pregnancy)*, a discussion between the investigator and the BMS Medical Monitor/designee must occur *so permission can be granted*.

All subjects who discontinue study drug should comply with protocol specified follow-up procedures as outlined in Section 5. The only exception to this requirement is when a subject withdraws consent for all study procedures 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) page.

3.6 Post Study Drug Study Follow up

PFS and OS are key endpoints of the study. Post treatment study follow-up is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study treatment prior to progression must continue to be followed for collection of protocol-defined PFS. Subjects who discontinue study therapy must also continue to be followed for overall survival data until death or the conclusion of the study.

BMS may request that survival data be collected on all treated/randomized subjects outside of the protocol defined window, Table 5.1-3. At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contacts or is lost to follow-up.

3.6.1 Withdrawal of Consent

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

3.6.2 Lost to Follow-Up

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

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and

databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 STUDY DRUG

Study drug includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) and can consist of the following:

Table 4.-1: Study Drugs for CA209602					
Product Description / Class and Dosage Form	**Potency**	**IP/Non-IP**	**Blinded or Open Label**	**Packaging / Appearance**	**Storage Conditions (per label)**
Nivolumab (BMS-936558-01) Solution for Injection[a]	100 mg (10 mg/mL)	IP	Open label	10 mL Vial/ Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect from light and freezing
Elotuzumab Powder for Solution for Infusion	400 mg/vial	IP	Open label	20 mL Vial/ Sterile, white to off-white, preservative-free, lyophilized cake	Store at 2°C - 8°C.
Dexamethasone Tablets[b]	2 mg and 4 mg & various strengths	Non-IP	Open label	Various packing configurations	Refer to label on container or package insert / summary of product characteristics
Dexamethasone Solution[b]	4 mg/mL, 8 mg/mL & various strengths	Non-IP	Open label	Various packing configurations	Refer to label on container or package insert / summary of product characteristics
Pomalidomide Capsules[b]	1 mg, 2 mg, 3 mg and 4 mg	Non-IP	Open label	Various packing configurations	Refer to label on container or package insert

[a] May be labeled as either “BMS-936558-01” or “Nivolumab.”

[b] Pomalidomide capsules, dexamethasone tablets and solution for IV infusion will be obtained by the investigating site’s standard prescribing procedures. They may be supplied by BMS according to country availability and specific regulatory requirements.

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.

In this protocol, investigational products are: nivolumab solution for IV infusion and elotuzumab powder for solution for infusion.

4.1.1 Elotuzumab

Before administration the drug product should be stored and prepared as per the instructions in pharmacy manual or elotuzumab investigator brochure. The dose of elotuzumab to be administered to a subject will be calculated by multiplying the subject's weight (kg) by 10 mg/kg (Cycles 1 through 4) and by 20 mg/kg (Cycles 5 and beyond). The subject's predose weight on Day 1 of each cycle will be used to calculate the dose for each cycle. Each dose should be infused as per instructions in the elotuzumab investigator brochure. The infusion start and stop time will be recorded in the CRF. If the infusion is stopped mid-session for any reason, the stop/start time must be recorded together with an explanation.

4.1.2 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 manual for guidelines on drug preparation and administration. Flush the intravenous line at the end of infusion

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: Pomalidomide (Pomalyst®) capsules 1 mg, 2 mg, 3 mg, and 4 mg, dexamethasone tablets and concentrate for solution for IV infusion, or products used for Elotuzumab premedication (Sections 4.5.1.3.6 and 4.5.1.3.7) or thromboprophylaxis (Section 3.4.2).

4.2.1 Pomalidomide

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

Because of this potential toxicity and to avoid fetal exposure to pomalidomide, pomalidomide is only available under a special restricted distribution program. Each risk management program is country or region specific. Under these programs, only prescribers and pharmacists registered with the program can prescribe and dispense the product. In addition, pomalidomide must only be dispensed to subjects who are registered and meet all the conditions of the local pomalidomide risk management program or meet all the conditions of the Pomalidomide Pregnancy Risk Prevention Plan (Appendix 6). Subjects who have the potential of pregnancy must be instructed about contraception and undergo the scheduled pregnancy tests.

Subjects should not break, chew or open the capsules. Pomalidomide should be taken in accordance with local label.

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

The trade name of pomalidomide may vary in other countries. In such cases, refer to country trade name.

4.2.2 Dexamethasone

Dexamethasone tablets and solution for IV infusion is considered Non-IP/Non-IMP for this study. Marketed product will be utilized for this study and should be stored in accordance with the package insert or summary of product characteristics (SmPC).

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.

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

Study drug not supplied by BMS need to 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).

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

Please refer to the current version of the IB and/or pharmacy manual for complete storage, handling, dispensing, and infusion information for nivolumab and elotuzumab.

Nivolumab vials must be stored at a temperature of 2°to 8°C and should be protected from light and freezing. Elotuzumab vials must be stored at a temperature of 2° to 8°C. If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

For details on prepared drug storage and use time of nivolumab and elotuzumab under room temperature/light and refrigeration, please refer to the nivolumab and elotuzumab IB section for "Recommended Storage and Use Conditions" and/or pharmacy manual.

4.4 Method of Assigning Subject Identification

4.4.1 Subject Identification

Subjects will be identified and informed consent obtained. Subjects must be enrolled into the study by the interactive web response system (IWRS) to obtain the subject number. The following information is required for subject enrollment:

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

Once it has been determined that a subject is eligible for randomization, the site will enter into the IWRS to obtain the treatment assignment. Subjects will be randomized to pomalidomide + dexamethasone + nivolumab (N-Pd investigational arm) or pomalidomide + dexamethasone (Pd Control arm) in a 1:1 ratio. The randomization will be carried out via permuted blocks within each stratum and stratified by the following factors:

a) number of lines of prior therapy (2 vs 3+)

b) ISS stage (1-2 vs. 3)

Additional details will be included in the IWRS manual including instructions for subjects at the time of cross-over to NE-Pd.

4.5 Selection and Timing of Dose for Each Subject

4.5.1 Treatment with Study Drugs

4.5.1.1 Arm A (N-Pd; Investigational arm)

Table 4.5.1.1-1: Arm A (N-Pd; Investigational arm)

Cycle (28 days)	Cycles 1 - 4					Cycles 5 and Beyond				
Day	**1**	**8**	**15**	**22**	**28**	**1**	**8**	**15**	**22**	**28**
Pomalidomide	Day 1-21					Day 1-21				
Dexamethasone	X	X	X	X		X	X	X	X	
Nivolumab[a]	X		X			X				

[a] Nivolumab dose is 240 mg during Cycles 1 - 4 then 480 mg during Cycles 5 and beyond

4.5.1.1.1 Pomalidomide

Administered orally at the dose of 4 mg daily on Days 1 - 21 of each 28 day cycle. Pomalidomide should be taken in accordance with local label.

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.

4.5.1.1.2 Dexamethasone

Table 4.5.1.1-2: Dexamethasone Dosing, All Cycles

Age	Day	1	8	15	22
≤ 75 years old	Dexamethasone (mg)	40 mg PO	40 mg PO	40 mg PO	40 mg PO
> 75 years old	Dexamethasone (mg)	20 mg PO	20 mg PO	20 mg PO	20 mg PO

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

4.5.1.1.3 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).

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. During cycles 5 and beyond, nivolumab can be delayed within a week. For subjects being dosed in the nivolumab 480 mg Q4W part of the study, for the first dose, it may be dosed no less than 12 days from the previous dose and for subsequent doses it should be dosed no less than 21 days from the previous dose. Nivolumab can be delayed within a 7 day window of Day 1 as long as the 12 day and 21 day intervals for the first 480 mg dose and subsequent 480 mg doses, respectively, between 2 nivolumab doses is respected. Doses that fall outside the allowed window should be skipped.

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 4.5.2.1.4.

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

4.5.1.2 Arm B (Pd; Control arm)

Table 4.5.1.2-1: Arm B (Pd; Control arm)

Cycle (28 days)	**All Cycles**				
Day	**1**	**8**	**15**	**22**	**28**
Pomalidomide	Day 1-21				
Dexamethasone	X	X	X	X	

4.5.1.2.1 Pomalidomide

Administered orally at the dose of 4 mg daily on Days 1 - 21 of each 28 day cycle. Pomalidomide should be taken in accordance with local label.

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

4.5.1.2.2 Dexamethasone

Table 4.5.1.2-2: Dexamethasone Dosing, All Cycles

Age	**Day**	**1**	**8**	**15**	**22**
≤ 75 years old	Dexamethasone	40 mg PO	40 mg PO	40 mg PO	40 mg PO

Table 4.5.1.2-2: Dexamethasone Dosing, All Cycles					
Age	**Day**	**1**	**8**	**15**	**22**
	(mg)				
> 75 years old	Dexamethasone (mg)	20 mg PO	20 mg PO	20 mg PO	20 mg PO

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

4.5.1.3 Arm C (NE-Pd; Exploratory arm)

Table 4.5.1.3-1: Treatment Schedule

Cycle (28 days)	Cycles 1 & 2					Cycles 3 & 4					Cycles 5 and Beyond				
Day	1	8	15	22	28	1	8	15	22	28	1	8	15	22	28
Pomalidomide	Day 1-21					Day 1-21					Day 1-21				
Dexamethasone	X	X	X	X		X	X	X	X		X	X	X	X	
Nivolumab[a]	X		X			X		X			X				
Elotuzumab[b]	X	X	X	X		X		X			X				

[a] Nivolumab dose is 240 mg during Cycles 1 - 4 then 480 mg during Cycles 5 and beyond

[b] Elotuzumab dose is 10 mg/kg during Cycles 1 - 4 then 20 mg/kg during Cycles 5 and beyond

4.5.1.3.1 Pomalidomide

Administered orally at the dose of 4 mg daily on Days 1 - 21 of each 28 day cycle. Pomalidomide should be taken in accordance with local label.

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.

4.5.1.3.2 Dexamethasone

Table 4.5.1.3-2: Dexamethasone Dosing, All Subjects Receiving Elotuzumab					
Age	**Day**	**1**	**8**	**15**	**22**
Cycles 1 and 2					
≤ 75 years old	Dexamethasone (mg)	28 mg PO + 8 mg IV	28 mg PO + 8 mg IV	28 mg PO + 8 mg IV	28 mg PO + 8 mg IV

Table 4.5.1.3-2: Dexamethasone Dosing, All Subjects Receiving Elotuzumab					
Age	**Day**	**1**	**8**	**15**	**22**
> 75 years old	Dexamethasone (mg)	8 mg PO + 8 mg IV	8 mg PO + 8 mg IV	8 mg PO + 8 mg IV	8 mg PO + 8 mg IV
Cycle 3 and 4					
≤ 75 years old	Dexamethasone (mg)	28 mg PO + 8 mg IV	40 mg PO	28 mg PO + 8 mg IV	40 mg PO
> 75 years old	Dexamethasone (mg)	8 mg PO + 8 mg IV	20 mg PO	8 mg PO + 8 mg IV	20 mg PO
Cycle 5 and Beyond					
≤ 75 years old	Dexamethasone (mg)	28 mg PO + 8 mg IV	40 mg PO	40 mg PO	40 mg PO
> 75 years old	Dexamethasone (mg)	8 mg PO + 8 mg IV	20 mg PO	20 mg PO	20 mg PO

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

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) (At the discretion of the investigator, the oral dexamethasone component may be given as a split dose 12 - 24 and 3 hours prior to elotuzumab), AND
- 8 mg IV (on the day of elotuzumab infusion at least 45 minutes before the start of infusion)

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

4.5.1.3.3 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.

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. During cycles 5 and

beyond, nivolumab can be delayed within a week. Doses that fall outside the allowed window 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 4.5.2.1.4.

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

4.5.1.3.4 Elotuzumab

Elotuzumab will be administered at a dose of 10 mg/kg as an intravenous infusion weekly (Days 1, 8, 15 and 22 of each 28 day cycle) during Cycles 1 and 2 then every 2 weeks (Days 1 and 15 of each 28 day cycle) during Cycles 3 and 4. Starting Cycle 5 and beyond, Elotuzumab will be administered at a dose of 20 mg/kg as an intravenous infusion every 4 weeks (Day 1 of each 28 day cycle).

Nivolumab should be administered first over 30 min followed by elotuzumab. The elotuzumab premedications can be administered before nivolumab infusion. There is no specific time interval needed between nivolumab and elotuzumab infusions.

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.

Table 4.5.1.3-3: Elotuzumab Dosing, All Subjects Receiving Elotuzumab

	Cycles 1 and 2			
DAY	**1**	**8**	**15**	**22**
Elotuzumab (IV)	10 mg/kg	10 mg/kg	10 mg/kg	10 mg/kg
	Cycle 3 and 4			
Elotuzumab (IV)	10 mg/kg		10 mg/kg	
	Cycle 5 and Beyond			
Elotuzumab (IV)	20 mg/kg			

4.5.1.3.5 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 Table 4.5.1.3-4.

Table 4.5.1.3-4: 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[a]
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

[a] 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.

4.5.1.3.6 Elotuzumab Premedication Regimen in Subjects Without a Prior Infusion Reaction

Consult the Medical Monitor for further guidance regarding alternative premedications for subjects allergic or intolerant to any premedication or to determine if locally used equivalent medications are acceptable.

On weeks of elotuzumab infusion, the dexamethasone dose will be split into a PO and IV administration 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).

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).

4.5.1.3.7 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 (premedications can be administered prior to nivolumab infusion in NE-Pd arm).

To prevent imbalance in dexamethasone exposure between the arms of the study, doses of intravenous dexamethasone above 10 mg require a decrease in the PO dexamethasone. Recommended dexamethasone dosing is summarized in Table 4.5.1.3-5.

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 4.5.1.3-5: 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

[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 premedicated as per Grade 2 infusion reactions.

[c] Subjects with prior Grade 2 infusion reaction may be premedicated 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, see Section 4.5.2.1.3.

4.5.2 Management of Infusion Reactions

4.5.2.1 Guidelines for Elotuzumab Infusion in Subjects with Infusion Reactions

4.5.2.1.1 Grade 1 Infusion Reaction

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

4.5.2.1.2 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 or per investigator's discretion) to the rate at which the infusion reaction occurred. If no recurrence of the infusion reaction, the escalation regimen according to the table above 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 (or as clinically indicated per investigator's discretion). 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 in Table 4.5.1.3-5**.**

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 above.

Elotuzumab infusions on subsequent weeks after a prior Grade 2 or 3 infusion reaction: Subjects with a prior Grade 2 or 3 infusion reaction during Cycle 1 should have the subsequent infusion started at 0.5 mL/min. The infusion rate may be 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.

Contact the Medical Monitor with any questions regarding elotuzumab infusion rate escalation.

4.5.2.1.3 Grade 4 Infusion Reaction

Acute symptoms should be managed as described in Section 4.5.2.1.2. Elotuzumab must be permanently discontinued. Subjects may continue with nivolumab, pomalidomide and dexamethasone per protocol.

4.5.2.1.4 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, arthalgias, 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 4.0) guidelines.

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

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

- 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 ventilatory support indicated):

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

4.5.3 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 5 and in the nivolumab Investigator Brochure.

4.5.4 Dose Delay, Interruption, or Discontinuation, All Subjects

If the dose of one drug in the regimen (ie, pomalidomide, dexamethasone, nivolumab or elotuzumab) is interrupted, or discontinued, the treatment with the other drugs may continue as scheduled. However, if dexamethasone is interrupted or discontinued discuss ongoing elotuzumab administration with the medical monitor (applicable for NE-Pd arm only).

Each cycle is 28 days. While dose delays (within the allowed window determined below for nivolumab and elotuzumab) or interruptions are permitted, the start of each cycle cannot be delayed and is fixed (ie, anchored) relative to Cycle 1 Day 1. Adjustments to the Cycle 1 Day 1 anchored schedule should not be performed. Should the start of a cycle be delayed, it is expected the following cycle begin as anchored to Cycle 1 Day 1. For example, if a subject is unable to start Cycle (X) until 3 days after the anchored start date, all assessments should be recorded on Cycle

(X) Day 3. The following cycle should begin on Day 1 (not Day 3) of Cycle (X+1). 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.

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

4.5.4.1 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.

4.5.4.2 Dexamethasone

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

For subjects receiving elotuzumab, 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 4.5.1.3.2.

4.5.4.3 Pomalidomide

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

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

4.5.4.4 Nivolumab

For subjects being dosed in the nivolumab 240 mg Q2W part of the study, they may be dosed no less than 12 days from the previous dose. Nivolumab can be delayed within a 3 day window of Day 1 and Day 15 as long as the 12 day interval between 2 nivolumab 240 mg doses is respected. Doses that fall outside the allowed window should be skipped.

For subjects being dosed in the nivolumab 480 mg Q4W part of the study, for the first dose, it may be dosed no less than 12 days from the previous dose and for subsequent doses it should be dosed no less than 21 days from the previous dose. Nivolumab can be delayed within a 7 day window of Day 1 as long as the 12 day and 21 day intervals for the first 480 mg dose and subsequent 480 mg

doses, respectively, between 2 nivolumab doses is respected. Doses that fall outside the allowed window should be skipped.

A pattern of immune-related AEs (IMAEs) has been defined in subjects treated with nivolumab, for which management algorithms have been developed. Appendix 5 includes these comprehensive algorithms for supportive care, by system organ and by severity (See Section 4.5.3).

4.5.4.4.1 Dose Delay/Interruption Criteria for Nivolumab

Nivolumab administration should be delayed for the following:

- Grade 2 non-skin, drug-related AE, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities
- Grade 3 skin, drug-related AE
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay
  - Grade ≥ 3 AST, ALT, Total Bilirubin will require dose discontinuation (see Section 4.5.4.4.3)
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

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

Additional criteria for nivolumab dose delay/interruption are included in the nivolumab IMAE management algorithm in Appendix 5.

4.5.4.4.2 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.
- For participants with Grade 2 AST, ALT and/or Total Bilirubin abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
- Drug-related pulmonary toxicity, diarrhea or colitis must have resolved to baseline before treatment is resumed. Participants 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 BMS Medical Monitor (or designee).

Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor (or

designee). Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

Dose delay/interruption of nivolumab which results in treatment interruption of > 8 weeks require treatment discontinuation, with exceptions as noted in Section 4.5.4.4.3. There will be no dose reductions for nivolumab.

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

* In most cases of Grade 3 AST or ALT elevation, study treatment will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

- Any Grade 4 drug-related adverse event or laboratory abnormality (including but not limited to creatinine, AST, ALT, or Total Bilirubin), except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 drug-related endocrinopathy adverse events, such as, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor.

- Any event that leads to delay in dosing lasting > 8 weeks from the previous dose requires discontinuation, with the following exceptions:
  - *Dosing delays to allow for prolonged steroid tapers to manage drug-related 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.
- At investigator's discretion, based on the safety results from the interim analysis and subject's derived clinical benefit (as of 23-Aug-2018).

Additional criteria for nivolumab dose discontinuation are included in the nivolumab IMAE management algorithm in Appendix 5.

4.5.5 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. Local standards may differ and may be followed. Dose modification may occur in the setting of lower grade toxicity if the investigator, in consultation with the Medical Monitor/Sponsor, believes that it is in the interest of subject safety.

4.5.5.1 Nivolumab and Elotuzumab

No dose reductions are allowed for nivolumab or elotuzumab.

4.5.5.2 Dexamethasone

Dexamethasone dose reductions for toxicity must be performed as clinically indicated. Recommended management is described in Table 4.5.5.2-1 and Table 4.5.5.2-2**.** Deviations to the recommended dose reductions are allowed based on the clinical judgment of the investigator.

Table 4.5.5.2-1: Dexamethasone Dose Reductions		
CTCAE Category	**Adverse Event**	**Treatment Adjustment**
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1 - 2 (requiring medical management)	Treat with a proton pump inhibitor. If symptoms persist despite above measures, decrease by 1 dose level.
	≥ Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms are adequately controlled. Reduce by 1 dose level and resume along with concurrent therapy with a proton pump inhibitor. If symptoms persist despite above measures, reduce to dose level -3 (dose withheld).
	Acute pancreatitis	Reduce to dose level -3 (dose withheld).
Cardiovascular	Edema ≥ Grade 3 (limiting function and unresponsive to therapy or anasarca)	Use diuretics as needed, and decrease dexamethasone by 1 dose level. If edema persists despite above measures, decrease by another dose level.
Neurology	Confusion or Mood alteration ≥ Grade 2 (interfering with function ± interfering with activities of daily living)	Hold dexamethasone until symptoms resolve. Decrease by 1 dose level and resume. If symptoms persist despite above measures, decrease by another dose level.
Musculoskeletal	Muscle weakness ≥ Grade 2 (symptomatic and interfering with function ± interfering with activities of daily living)	Hold dose until muscle weakness is ≤ Grade 1. Decrease dexamethasone by 1 dose level and resume. If weakness persists despite above measures, decrease by another dose level.
Metabolic	Hyperglycemia ≥ Grade 3 or higher	Treat with insulin or oral hypoglycemics as needed. If uncontrolled despite above measures, decrease by 1 dose level until glucose levels are satisfactory.
Constitutional	Insomnia ≥ Grade 2	Decrease by 1 dose level and resume.

Dose reduction for persistent Grade 2 or Grade ≥ 3 AEs believed to be related to dexamethasone and not listed above are permitted. Dose reductions should follow the guidance in Table 4.5.5.2-1 and Table 4.5.5.2-2.

For subjects receiving elotuzumab, regardless of dexamethasone dose reduction, at least 8 mg of the weekly dexamethasone dose must be administered IV as part of the premedication for elotuzumab with the remainder of the weekly dexamethasone dose administered orally as described in Section 4.5.1.3.2. Contact the Medical Monitor to discuss dexamethasone IV premedication for subjects in the investigational arm who reach dose level -3 and must discontinue dexamethasone due to dose limiting toxicity.

On days without elotuzumab, no IV dexamethasone should be administered.

Table 4.5.5.2-2: 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	8 mg	≤ 75 years old - 40 mg	N/A
	> 75 years old - 8 mg		> 75 years old - 20 mg	
-1	≤ 75 years old - 12 mg	8 mg	≤ 75 years old - 20 mg	N/A
	> 75 years old - 2 mg		> 75 years old - 12 mg	
-2	≤ 75 years old - 0 mg	8 mg	≤ 75 years old - 12 mg	N/A
	> 75 years old - 0 mg		> 75 years old - 8 mg	
-3	≤ 75 years old - 0 mg	Contact Medical Monitor	≤ 75 years old - 0 mg	N/A
	> 75 years old - 0 mg		> 75 years old - 0 mg	

4.5.5.3 Pomalidomide

Below are the recommended dose adjustments for the management of thrombocytopenia and neutropenia judged by the investigator to be related to pomalidomide. Information in Table 4.5.5.3-1 and Table 4.5.5.3-2 is based on pomalidomide prescribing information, which contains additional guidance on pomalidomide dosing [28,29]. Investigators should follow the guidelines in the prescribing information for pomalidomide. Some clinically relevant events and their management are presented below.

Table 4.5.5.3-1: Treating Thrombocytopenia Related to Pomalidomide	
When Platelet Count:	**Recommended Course:**
• Fall to < 25,000 per mm^3 • Return to > 50,000 per mm^3	• Interrupt pomalidomide treatment, follow Complete Blood Count weekly. • Resume pomalidomide at 3 mg daily
• For each subsequent drop < 25,000 mm^3 • Return to ≥ 50,000 mm^3	• Interrupt pomalidomide treatment • Resume pomalidomide at 1 mg less than previous dose

Table 4.5.5.3-2: 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) • ANC returns to ≥ 1000 per mm^3	• Interrupt pomalidomide treatment, follow Complete Blood Count weekly. • Resume pomalidomide at 3 mg daily
• For each subsequent drop < 500 mm^3 • Return to ≥ 1000 mm^3	• Interrupt pomalidomide treatment • Resume pomalidomide at 1 mg less than previous dose

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

If necessary to co-administer strong inhibitors of CYP1A2 in the presence of strong inhibitors of CYP3A4 and P-glycoprotein, consider reducing pomalidomide dose by 50%.[28,29]

4.6 Blinding/Unblinding

Not applicable

4.7 Treatment Compliance

Treatment compliance will be monitored by drug accountability and recorded in the subject's medical record and CRF. 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.

4.10 Retained Samples for Bioavailability / Bioequivalence

Not applicable.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Procedural Outline (CA209602) - All Subjects

Procedure	Screening Visit	Use of Central (CL) or Local (LL) Lab	Notes
Eligibility Assessments			
Informed Consent	X		Prior to any screening procedures (note: any procedure/lab done before ICF signed would be acceptable if part of standard of care)
Inclusion/Exclusion Criteria	X		Within 14 days of randomization
Medical History	X		Includes date and ISS Stage at initial diagnosis of MM (Within 28 days of randomization)
International Staging System (ISS) stage at study entry[31]	X		Appendix 4
Safety Assessments			
Physical Examination	X		Full physical examination, including weight, within 14 days of randomization - Section 5.3.2
Vital Signs	X		Temperature, BP, HR within 14 days of randomization - Section 5.3.2
Performance Status (ECOG)	X		Evaluate prior to dosing (Appendix 2) within 14 days of randomization
Serious Adverse Events Assessment	X		Collected from the time of informed consent
Second Primary Malignancy	X		Collected from the time of informed consent - Section 6.7
Concomitant Medications	X		Within 14 days of randomization
ECG	X	LL	Within 28 days of randomization - Section 5.3.4
Laboratory Assessments			
CBC, Differential, Platelets	X	LL	Within 14 days of randomization - Section 5.3.5
Hepatitis B surface antigen (HBV sAg), and hepatitis C antibody	X	LL	Within 28 days of randomization - Section 5.3.5

Table 5.1-1: Screening Procedural Outline (CA209602) - All Subjects			
Procedure	**Screening Visit**	**Use of Central (CL) or Local (LL) Lab**	**Notes**
(HCV Ab) or HCV ribonucleic acid (RNA)			
Serum Chemistry	X	LL	Within 14 days of randomization - Section 5.3.5
Thyroid stimulating hormone (TSH) (reflex to free T3/total T3, free T4 for abnormal TSH result)	X	LL	Within 28 days of randomization - Section 5.3.5
Creatinine Clearance Assessment	X	LL	By Cockcroft-Gault within 14 days of randomization (Section 3.3.2 for calculation)
Pregnancy Test	X	LL	**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 ≥ 25 mIU/mL
Serum β2-microglobulin	X	CL	Within 28 days of randomization. Central lab analysis for stratification
Serum Albumin	X	CL	Within 28 days of randomization. Central lab analysis for stratification
Efficacy Assessments [redacted]			
Myeloma Urine and Serum Lab tests (SPEP/UPEP/sFLC)	X	CL	Section 5.4.2 Within 28 days of randomization; Central Laboratory analysis; Results must be available prior to first dose of study drug

Table 5.1-1: Screening Procedural Outline (CA209602) - All Subjects			
Procedure	**Screening Visit**	**Use of Central (CL) or Local (LL) Lab**	**Notes**
Bone Marrow Aspirate	X	LL	Section 5.4.2 Bone Marrow aspirate is mandatory. Bone marrow biopsy is optional. Bone marrow biopsy is required if an aspirate sample (at any required time point) is not available due to a dry tap. Plasma cell percentage is required and should be performed locally per institution standard practice, within 35 days of randomization.
	X	CL	Section 5.4.2 and Table 5.4.2-1 **Bone Marrow aspirate is mandatory.** Collections are required at screening, ≥VGPR, and every 6 Cycles thereafter until PD. In subjects with confirmed PD, collection is optional upon PD confirmation.
Corrected Calcium	X	LL	Section 5.4.2; Within 14 days of randomization; Results must be available prior to first dose of study drug.
Skeletal Survey	X	LL	Section.5.4.3.1 Within 28 days of randomization
CT or MRI assessment for extramedullary soft tissue plasmacytoma	X	LL	Section 5.4.3.2 Within 28 days of randomization, if subject had a previous extramedullary or bone plasmacytoma
[redacted]			
Clinical Drug Supplies			
Randomize	X		First dose of study drug must occur within 5 days of randomization.

Table 5.1-2: Procedural Outline (CA209602) Procedures Cycles 1 & 2 - All Subjects							
Procedure	**Local Lab (LL) or Central Lab (CL)**	**Day 1**	**Day 8***	**Day 15**	**Day 22***	**Rest Days 23-28**	**Notes (within 72 hours prior to dosing) * Day 8 & 22 pertain to the NE-Pd arm only**
Safety Assessments							
Targeted Physical Examination		X					Section 5.3.2 Perform prior to dosing, include weight
Vital Signs		X	X	X	X		Section 5.3.2 Temperature, BP, HR. Additional vital signs needed for Cycle 1 for NE-Pd arm as described in section 5.3.2
Performance Status (ECOG)		X					If performed and recorded at screening, to be done on C2D1 only. (Appendix 2)
Serious Adverse Events 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					Section 6.7
Laboratory Tests for Safety							***DAY 8 & 22 only pertain to the NE-Pd arm**
CBC & Differential	LL	X	X	X	X		Section 5.3.5 Can be drawn up to 3 days prior to dosing
Serum Chemistry	LL	X					Section 5.3.5 If performed and recorded at screening, to be done on C2D1 only. Can be drawn up to 3 days prior to dosing.

Table 5.1-2: Procedural Outline (CA209602) Procedures Cycles 1 & 2 - All Subjects							
Procedure	**Local Lab (LL) or Central Lab (CL)**	**Day 1**	**Day 8***	**Day 15**	**Day 22***	**Rest Days 23-28**	**Notes (within 72 hours prior to dosing) * Day 8 & 22 pertain to the NE-Pd arm only**
Thyroid function test	LL	X*					TSH (reflex to free T3/Total T3 and free T4 if abnormal result) to be performed every ***2 cycles** (± 7 days) from first dose regardless of dosing schedule (at screening, C2D1, C4D1, C6D1....etc).
Pregnancy Test	LL	X	X	X	X		Section 5.3.5 **For WOCBP only**. Urine tests must have a sensitivity of at least 25 mIU/mL. Weekly test within 24 hours of study medication
Efficacy Assessments							
Myeloma Urine and Serum Lab tests (SPEP/UPEP/sFLC)	CL	Every 4 weeks from date of first dose of study therapy **until confirmed disease progression**, regardless of whether subject is on study therapy or subsequent therapy.					Section 5.4.2 Day 1 of each cycle (including Cycle 1) until confirmed disease progression, even if subject is on subsequent therapy. 24- hour urine sample can be collected within ± 7 days of visit, and must be obtained in all subjects
Bone marrow aspirate	LL	See note					Section 5.4.2 Bone Marrow aspirate is mandatory. Bone marrow biopsy is optional. Bone marrow biopsy is required if an aspirate sample (at any required time point) is not available due to a dry tap. Collections are required at screening, ≥VGPR, and every 6 Cycles thereafter until PD. In subjects with confirmed PD, collection is optional upon PD confirmation. Evaluation of percentage of plasma cells and clonality is required and should be performed locally per institution standard practice.
	CL	See note					Section 5.4.2 and Table 5.4.2-1 Collections are required at screening, ≥VGPR, and every 6 Cycles thereafter until PD. In subjects with confirmed PD, collection is optional upon PD confirmation.

Table 5.1-2: Procedural Outline (CA209602) Procedures Cycles 1 & 2 - All Subjects							
Procedure	**Local Lab (LL) or Central Lab (CL)**	**Day 1**	**Day 8***	**Day 15**	**Day 22***	**Rest Days 23-28**	**Notes (within 72 hours prior to dosing) * Day 8 & 22 pertain to the NE-Pd arm only**
Corrected Calcium	LL	Every 4 weeks from date of first dose of study therapy **until confirmed disease progression**, regardless of whether subject is on study therapy or subsequent therapy.					Serum calcium and albumin from peripheral blood at D1 of each cycle until confirmed disease progression, even if subject is on subsequent therapy
Skeletal Survey	LL	If clinically indicated					See Section 5.4.3.1
CT/MRI Assessment of Extramedullary Soft Tissue plasmacytoma	LL	As clinically indicated					Section 5.4.3.2 (in subjects with baseline plasmacytoma, imaging follow-up should be done regularly per investigator's discretion). Imaging confirmation of disappearance of plasmacytoma is required at time of CR/sCR if it was not confirmed before.
Response Assessment (Per IMWG)		Every 4 weeks from date of first dose of study drug **until confirmed progression** regardless of whether on study therapy or subsequent therapy.					Section 5.4.1 Response assessments (≥ PR) and PD require confirmation (2 consecutive assessment)s (Appendix 3).
[redacted]							

Table 5.1-2: Procedural Outline (CA209602) Procedures Cycles 1 & 2 - All Subjects							
Procedure	**Local Lab (LL) or Central Lab (CL)**	**Day 1**	**Day 8***	**Day 15**	**Day 22***	**Rest Days 23-28**	**Notes (within 72 hours prior to dosing) * Day 8 & 22 pertain to the NE-Pd arm only**
Dosing							***DAY 8 & 22 only pertain to the NE-Pd arm**
Premedication for Elotuzumab (Elotuzumab Arm Subjects Only)		X	X	X	X		Sections 4.5.1; Nivolumab is infused before elotuzumab in the NE-Pd arm. Elotuzumab premedications can be administered before nivolumab infusion.
Elotuzumab Infusion		X	X	X	X		Section 4.5.1.3 for Elotuzumab window; Nivolumab is infused first on the NE-Pd arm
Nivolumab Infusion		X		X			Section 4.5.1. Nivolumab is infused first on the NE-Pd arm
Pomalidomide Administration		Day 1 - 21 of cycle					Dispense pomalidomide on Day 1 of each cycle per the local risk management program or the Pomalidomide Pregnancy Risk Prevention Plan (Appendix 6).
Dexamethasone Administration		X	X	X	X		Dexamethasone dosing per Section 4.5.1.
[redacted]							

Table 5.1-2: Procedural Outline (CA209602) Procedures Cycles 1 & 2 - All Subjects							
Procedure	**Local Lab (LL) or Central Lab (CL)**	**Day 1**	**Day 8***	**Day 15**	**Day 22***	**Rest Days 23-28**	**Notes (within 72 hours prior to dosing) * Day 8 & 22 pertain to the NE-Pd arm only**
[redacted]							

Table 5.1-3: Procedural Outline (CA209602) Cycles 3 and 4							
Procedure	**Local Lab (LL) or Central Lab (CL)**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Rest Days 23-28**	**Notes (within 72 hours prior to dosing)**
Safety Assessments							
Targeted Physical Examination		X					Section 5.3.2 Perform prior to dosing, include weight
Vital Signs		X		X			Section 5.3.2
Performance Status (ECOG)		X					Appendix 2 Evaluate prior to dosing
Serious Adverse Events Assessment		X		X			Evaluate prior to dosing *NSAEs and SAEs must be collected up to **100 days** after study drug discontinuation. SAEs related to any later protocol-specified procedure must be collected.
Adverse Events Assessment		X		X			Evaluate prior to dosing *NSAEs and SAEs must be collected up to **100 days** after study drug discontinuation. SAEs related to any later protocol-specified procedure must be collected.
Second Primary Malignancy		X					Section 6.7 30 and 100 day assessments may be performed ± 1 week. Follow-up: Assess every **12 weeks** (± 2 weeks), or more frequently.
Concomitant Medications		X					Evaluate prior to dosing
Laboratory Assessments							
CBC & Differential	LL	X					Section 5.3.5 Can be drawn up to 3 days prior to dosing

Table 5.1-3: Procedural Outline (CA209602) Cycles 3 and 4

Procedure	Local Lab (LL) or Central Lab (CL)	Day 1	Day 8	Day 15	Day 22	Rest Days 23-28	Notes (within 72 hours prior to dosing)
Serum Chemistry	LL	X					Section 5.3.5 Can be drawn up to 3 days prior to dosing
Thyroid function test	LL	X*					TSH (reflex to free T3/Total T3 and free T4 if abnormal result) to be performed every ***2 cycles** (± 7 days) from first dose regardless of dosing schedule.
Pregnancy Test	LL	X					Sections 5.3.5 & 6.4 **For WOCBP only**. Tests must occur within 24 hours prior to dosing. If irregular menstrual cycles the pregnancy test should occur on Days 1 and 15 of each cycle. Urine tests must have a sensitivity of at least 25 mIU/mL *WOCBP must have a pregnancy test 30 and 100 days post end of treatment
Efficacy Assessments							
Myeloma Urine and Serum Lab tests (SPEP/UPEP/sFLC)	CL	Every 4 weeks from date of the first dose of study drug therapy **until confirmed disease progression**, regardless of whether subject is on study therapy or subsequent therapy.					See Section 5.4.2 Day 1 of each cycle until confirmed disease progression, even if subject is on subsequent therapy. 24-hour urine sample can be collected within ± 7 days of visit, and must be obtained in all subjects
Corrected Calcium	LL	Every 4 weeks from date of the first dose of study drug therapy **until confirmed disease progression**, regardless of whether subject is on study therapy or subsequent therapy.					Serum calcium and albumin from peripheral blood at D1 of each cycle until confirmed disease progression, even if subject is on subsequent therapy**.**

Table 5.1-3: Procedural Outline (CA209602) Cycles 3 and 4							
Procedure	**Local Lab (LL) or Central Lab (CL)**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Rest Days 23-28**	**Notes (within 72 hours prior to dosing)**
Bone Marrow Aspirate	CL	See Note					Section 5.4.2 and Table 5.4.2-1 **Bone Marrow aspirate is mandatory.** Collections are required at screening, ≥VGPR, and every 6 Cycles thereafter until PD. In subjects with confirmed PD, collection is optional upon PD confirmation.
Bone Marrow Aspirate	LL	See Note					Section 5.4.2 Bone Marrow aspirate is mandatory. Bone marrow biopsy is optional. Bone marrow biopsy is required if an aspirate sample (at any required time point) is not available due to a dry tap. Collections are required at screening, ≥VGPR, and every 6 Cycles thereafter until PD. In subjects with confirmed PD, collection is optional upon PD confirmation. Evaluation of percentage of plasma cells and clonality is required and should be performed locally per institution standard practice.
Skeletal Survey	LL	If clinically indicated.					Section 5.4.3.1
CT/MRI Assessment of Extramedullary Soft Tissue plasmacytoma	LL	As clinically indicated					Section 5.4.3.2 (in subjects with baseline plasmacytoma, imaging follow-up should be done regularly per investigator's discretion). Imaging confirmation of

Table 5.1-3: Procedural Outline (CA209602) Cycles 3 and 4							
Procedure	**Local Lab (LL) or Central Lab (CL)**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Rest Days 23-28**	**Notes (within 72 hours prior to dosing)**
							disappearance of plasmacytoma is required at time of CR/sCR if it was not confirmed before
Response Assessment Per IMWG		Every 4 weeks from date of first dose of study drug **until confirmed progression** regardless of whether on study therapy or subsequent therapy.					Section 5.4.1 Response assessments (≥ PR) and PD require confirmation (2-consecutive assessments) (Appendix 3).
[redacted]							
Dosing							
Premedication for Elotuzumab (Elotuzumab Arm Subjects Only)		X		X			Sections 4.5.1, Nivolumab is infused first on the NE-Pd arm
Elotuzumab Infusion		X		X			Section 4.5.5.1 for Elotuzumab window, Nivolumab is infused before elotuzumab in the NE-Pd arm. Elotuzumab premedications can be administered before nivolumab.
Nivolumab Infusion		X		X			Section 4.5.1, Nivolumab is infused first on the NE-Pd arm

Table 5.1-3: Procedural Outline (CA209602) Cycles 3 and 4							
Procedure	**Local Lab (LL) or Central Lab (CL)**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Rest Days 23-28**	**Notes (within 72 hours prior to dosing)**
Pomalidomide Administration		Day 1 - 21 of Cycle					Dispense pomalidomide on Day 1 of each cycle per the local risk management program or the Pomalidomide Pregnancy Risk Prevention Plan (Appendix 6).
Dexamethasone Administration		X	X	X	X		Dexamethasone dosing per Section 4.5.1.2
[redacted]							

Table 5.1-4: Procedural Outline (CA209602) Cycles 5 and Beyond										
Procedure	**Local Lab (LL) or Central Lab (CL)**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Rest Days 23-28**	**End Of Treatment**	**Follow up visits: Days 30 & 100 post end of treatment (+/- 7 day window**	**Survival Follow-Up (+/-14 day window)**	**Notes**
Safety Assessments										
Targeted Physical Examination		X					X			Section 5.3.2 Perform prior to dosing, include weight
Vital Signs		X					X			Section 5.3.2
Performance Status (ECOG)		X					X			Appendix 2 Evaluate prior to dosing
Serious Adverse Events Assessment		X					X	X*		Evaluate prior to dosing *NSAEs and SAEs must be collected up to **100 days** after study drug discontinuation. SAEs related to any later protocol-specified procedure must be collected.
Adverse Events Assessment		X					X	X*		Evaluate prior to dosing *NSAEs and SAEs must be collected up to **100 days** after study drug discontinuation. SAEs related to any later protocol-specified procedure must be collected.

Table 5.1-4: Procedural Outline (CA209602) Cycles 5 and Beyond										
Procedure	**Local Lab (LL) or Central Lab (CL)**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Rest Days 23-28**	**End Of Treatment**	**Follow up visits: Days 30 & 100 post end of treatment (+/- 7 day window**	**Survival Follow-Up (+/-14 day window)**	**Notes**
Second Primary Malignancy		X					X	X	X	Section 6.7 30 and 100 day assessments may be performed ± 1 week. Follow-up: Assess every **12 weeks** (± 2 weeks), or more frequently.
Concomitant Medications		X					X	X		Evaluate prior to dosing
Subsequent Myeloma Therapy							X	X	X	30 and 100 day assessments may be performed ± 1 week, Follow-up: Assess every **12 weeks** (± 2 weeks), or more frequently.
Laboratory Assessments										
CBC & Differential	LL	X					X	X		Section 5.3.5 Can be drawn up to 3 days prior to dosing
Serum Chemistry	LL	X					X	X		Section 5.3.5 Can be drawn up to 3 days prior to dosing

Table 5.1-4: Procedural Outline (CA209602) Cycles 5 and Beyond										
Procedure	**Local Lab (LL) or Central Lab (CL)**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Rest Days 23-28**	**End Of Treatment**	**Follow up visits: Days 30 & 100 post end of treatment (+/- 7 day window**	**Survival Follow-Up (+/-14 day window)**	**Notes**
Thyroid function test	LL	X*					X	X		TSH (reflex to free T3/Total T3 and free T4 if abnormal result) to be performed every ***2 cycles** (± 7 days) from first dose regardless of dosing schedule.
Pregnancy Test	LL	X					X	X*		Sections 5.3.5 & 6.4 **For WOCBP only**. Tests must occur within 24 hours prior to dosing. Urine tests must have a sensitivity of at least 25 mIU/mL *WOCBP must have a pregnancy test 30 and 100 days post end of treatment

Table 5.1-4: Procedural Outline (CA209602) Cycles 5 and Beyond										
Procedure	**Local Lab (LL) or Central Lab (CL)**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Rest Days 23-28**	**End Of Treatment**	**Follow up visits: Days 30 & 100 post end of treatment (+/- 7 day window**	**Survival Follow-Up (+/-14 day window)**	**Notes**
Efficacy Assessments										
Myeloma Urine and Serum Lab tests (SPEP/UPEP/sFLC)	CL	Every 4 weeks from date of the first dose of study drug therapy **until confirmed disease progression,** regardless of whether subject is on study therapy or subsequent therapy.								See Section 5.4.2 Day 1 of each cycle until confirmed disease progression, even if subject is on subsequent therapy. 24-hour urine sample can be collected within ± 7 days of visit, and must be obtained in all subjects.
Corrected Calcium	LL	Every 4 weeks from date of the first dose of study drug therapy **until confirmed disease progression,** regardless of whether subject is on study therapy or subsequent therapy.								Serum calcium and albumin from peripheral blood at D1 of each cycle until confirmed disease progression, even if subject is on subsequent therapy
Bone Marrow Aspirate	CL	See note								Section 5.4.2 and Table 5.4.2-1 **Bone Marrow aspirate is mandatory.** Collections are required at screening, ≥VGPR, and every 6 Cycles thereafter until PD. In subjects with confirmed PD, collection is optional upon PD confirmation.

Table 5.1-4: Procedural Outline (CA209602) Cycles 5 and Beyond

Procedure	Local Lab (LL) or Central Lab (CL)	Day 1	Day 8	Day 15	Day 22	Rest Days 23-28	End Of Treatment	Follow up visits: Days 30 & 100 post end of treatment (+/- 7 day window	Survival Follow-Up (+/-14 day window)	Notes
Bone Marrow Aspirate	LL	See note								Section 5.4.2 Bone Marrow aspirate is mandatory. Bone marrow biopsy is optional. Bone marrow biopsy is required if an aspirate sample (at any required time point) is not available due to a dry tap. Collections are required at screening, ≥VGPR, and every 6 Cycles thereafter until PD. In subjects with confirmed PD, collection is optional upon PD confirmation. Evaluation of percentage of plasma cells and clonality is required and should be performed locally per institution standard practice.
Skeletal Survey	LL	If clinically indicated.								Section 5.4.3.1
CT/MRI Assessment of Extramedullary Soft Tissue plasmacytoma	LL	As clinically indicated								Section 5.4.3.2 (in subjects with baseline plasmacytoma, imaging follow-up should be done regularly per investigator's discretion). Imaging confirmation of disappearance of plasmacytoma is required at time of CR/sCR if it was not confirmed before

Table 5.1-4: Procedural Outline (CA209602) Cycles 5 and Beyond										
Procedure	**Local Lab (LL) or Central Lab (CL)**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Rest Days 23-28**	**End Of Treatment**	**Follow up visits: Days 30 & 100 post end of treatment (+/- 7 day window**	**Survival Follow-Up (+/-14 day window)**	**Notes**
Response Assessment Per IMWG		Every 4 weeks from date of first dose of study drug **until confirmed progression** regardless of whether on study therapy or subsequent therapy.								Section 5.4.1 Response assessments (≥ PR) and PD require confirmation (2-consecutive assessments) (Appendix 3).
[redacted]										
Survival Status								X	X	30 and 100 day visits may be performed ± 1 week, Follow-up: Assess every **12 weeks** (± 2 weeks), or more frequently
Dosing										
Premedication for Elotuzumab (Elotuzumab Arm Subjects Only)		X								Sections 4.5.1, Nivolumab is infused first on the NE-Pd arm

Table 5.1-4: Procedural Outline (CA209602) Cycles 5 and Beyond										
Procedure	**Local Lab (LL) or Central Lab (CL)**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Rest Days 23-28**	**End Of Treatment**	**Follow up visits: Days 30 & 100 post end of treatment (+/- 7 day window**	**Survival Follow-Up (+/-14 day window)**	**Notes**
Elotuzumab Infusion		X								Section 4.5.1 for Elotuzumab window, Nivolumab is infused before Elotuzumab in the NE-Pd arm/Elotuzumab premedications can be administered before nivolumab.
Nivolumab Infusion		X								Section 4.5.1 Nivolumab is infused first on the NE-Pd arm
Pomalidomide Administration		Day 1 - 21 of Cycle								Dispense pomalidomide on Day 1 of each cycle per the local risk management program or the Pomalidomide Pregnancy Risk Prevention Plan (Appendix 6).
Dexamethasone Administration		X	X	X	X					Dexamethasone dosing per Section 4.5.1

Table 5.1-4: Procedural Outline (CA209602) Cycles 5 and Beyond										
Procedure	**Local Lab (LL) or Central Lab (CL)**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Rest Days 23-28**	**End Of Treatment**	**Follow up visits: Days 30 & 100 post end of treatment (+/- 7 day window**	**Survival Follow-Up (+/-14 day window)**	**Notes**
[redacted]										

Table 5.1-4: Procedural Outline (CA209602) Cycles 5 and Beyond										
Procedure	**Local Lab (LL) or Central Lab (CL)**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Rest Days 23-28**	**End Of Treatment**	**Follow up visits: Days 30 & 100 post end of treatment (+/- 7 day window**	**Survival Follow-Up (+/-14 day window)**	**Notes**
[redacted]										

5.1.1 Retesting During Screening or Lead-in Period

Retesting of laboratory parameters and/or other assessments within any single screening 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 Randomization) 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 Table 5.1-1, 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:

- NCI CTCAE booklets version 4.0
- Elotuzumab Investigator Brochure
- Nivolumab Investigator Brochure
- Pomalidomide (Pomalyst®) Package Insert
- Site Manual for operation of IWRS
- Subject Dosing Diary
- Subject Quality of Life Questionnaires
- Serious Adverse Event (SAE) Case Report Form (CRF) pages
- Pregnancy Surveillance Forms
- Pharmacy Binder
- Laboratory manuals for collection and handling of blood samples
- Laboratory manual for local lab data entry

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 collected at least once per cycle.

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

5.3.1 Assessments 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, seated blood pressure, heart rate will be recorded as outlined in Table 5.1-1, Table 5.1-2, Table 5.1-3, and Table 5.1-4. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes prior to dosing. Subjects will have vital signs measured once at each visit. Subjects randomized to the NE-Pd arm will have *additional* vital signs during Cycle 1 only, as follows:

- Prior to pre-medication administration
- Prior to the start of the elotuzumab infusion
- Thirty minutes after the start of elotuzumab infusion
- At the end of the elotuzumab infusion
- Post infusion vital signs will be measured at 30 minutes.
- Subjects who experience a Grade ≥ 2 infusion reaction require vital signs to be monitored every 30 minutes for 1 - 2 hours after the end of the elotuzumab infusion (at the investigator's discretion).

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.

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, and Table 5.1-4 using ECOG performance scale and criteria as described in Appendix 2. The assessment should be completed prior to any study-related procedures, treatment or clinician assessment.

5.3.4 Cardiac Assessments

ECG will be performed at screening within 28 days of randomization.

5.3.5 Laboratory Assessments for Safety

Laboratory assessments for safety will be performed at local laboratories. Safety laboratory assessments are listed in Table 5.3.5-1.

Table 5.3.5-1: Safety Laboratory Assessments

Safety Laboratory Assessments		
	Screening as outlined in Table 5.1-1 Within 14 days of randomization	**Study Visits as outlined in Table 5.1-2 and Table 5.1-3**
Serum Hematology		
CBC	X	X
Differential (absolute counts: neutrophils, lymphocytes, monocytes, basophils, eosinophils)	X	X
Serum Chemistry		
Sodium	X	X
Potassium	X	X
Chloride	X	X
Carbon Dioxide or Bicarbonate[a]	X	X
Albumin	X	X
Alkaline Phosphatase	X	X
ALT (SGPT)	X	X
AST (SGOT)	X	X
Total Bilirubin	X	X
Direct Bilirubin[b]	X	
Lactate Dehydrogenase	X	X
BUN (or Urea)	X	X
Creatinine	X	X
Glucose	X	X
Calcium	X	X
Magnesium	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
Additional Assessments		
Hepatitis B surface antigen (HBV sAg), and hepatitis C antibody (HCV Ab) or HCV ribonucleic acid (RNA)	X[c]	

Table 5.3.5-1: Safety Laboratory Assessments

Safety Laboratory Assessments		
	Screening as outlined in Table 5.1-1 Within 14 days of randomization	**Study Visits as outlined in Table 5.1-2 and Table 5.1-3**
Thyroid stimulating hormone (TSH) (reflex to free T3/Total T3, free T4 for abnormal TSH result)	X[c]	X[d]

[a] To be done in sites where this is a standard part of the chemistry panel. In sites where testing for CO2/HCO3 is not standard, the test is optional

[b] Only required for subjects with Gilbert's Syndrome. See Section 3.3.2

[c] Within 28 days of randomization

[d] TSH (reflex to free T3/Total T3 and free T4 if abnormal result) to be performed every ***2 cycles** (± 7 days) from first dose regardless of dosing schedule (at screening, C2D1, C4D1, C6D1...etc).

5.4 Efficacy Assessments

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

IMWG Response criteria in Appendix 3 will be used for the efficacy analysis. For the purposes of this study, all subjects' tumor assessments by myeloma laboratory tests (SPEP M protein and UPEP M protein quantification, corrected calcium (calcium and albumin), and serum free light chain) should be re-evaluated per the protocol-stated frequency relative to the date of first dose of study drug until confirmed disease progression based on Appendix 3, irrespective of dose delays or treatment cycle. **If subject does not have documented disease progression as defined in Appendix 3 at the time of study drug discontinuation, then disease assessments must continue to be performed according to the same schedule described above until confirmed disease progression even if a subsequent anti-myeloma treatment is initiated prior to disease progression confirmation.** Subjects will be followed every 12 weeks, or more frequently, after disease progression for survival, subsequent myeloma therapy, and development of second primary malignancy.

All efficacy laboratory assessments (SPEP, UPEP, serum/urine immunofixation, and sFLC) 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). All bone marrow aspirate and core biopsy samples for

disease assessment should be assessed locally. [redacted] For any SPEP, UPEP, or sFLC assessment performed locally, in lieu of a central lab assessment, (ie, if the subject cannot complete a visit at the study site after treatment discontinuation), M protein absolute quantification (eg, g/dL or g/L) or sFLC (eg, mg/L or mg/dL) must be performed. Any laboratory samples analyzed locally, including for efficacy, must be entered on the appropriate CRF/eCRF as requested by the Sponsor to properly assess efficacy per protocol criteria.

5.4.2 Laboratory Assessments for Myeloma

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

Elotuzumab may be detected in the serum protein electrophoresis (SPEP) and serum immunofixation assays of myeloma patients and could interfere with correct response classification. A small peak in the early gamma region on SPEP that is IgGκ on serum immunofixation may potentially be attributed to elotuzumab, particularly in patients whose endogenous myeloma protein is IgA, IgM, IgD, or lambda light chain restricted. This interference can impact the determination of complete response and possibly relapse from complete response in patients with IgG kappa myeloma protein. It is likely that nivolumab may also be detected by SPEP and immunofixation but this is still under investigation. Serum or peripheral blood samples, collected during the study, may be analyzed for the presence of monoclonal antibody interference.

1) **Serum**: SPEP for M protein quantification, total serum protein, serum immunofixation, and quantitative immunoglobulin assay.
   a. Serum Immunofixation (IFE) is required at baseline and to confirm CR regardless of whether measurable M-protein was present at baseline.
   b. Subjects with measurable disease in SPEP will be assessed for response based on SPEP and not by the serum FLC assay.
   c. Subjects with measurable disease in both SPEP and UPEP will be assessed for response based on these two tests and not by the serum FLC assay.
   d. Subjects with FLC only disease (i.e. serum and urine IFE negative) should be monitored by sFLC only; SPEP, UPEP and IFE are required only to code CR in those subjects
   e. Subjects with measurable disease by sFLC only, but with non-measurable serum M-protein, will be monitored by sFLC assay for response. However, their SPEP should also be monitored for progression.
2) **Serum free light chain (sFLC)**:
   a. Subjects without measurable serum M-protein (ie, < 0.5 g/dL (5 g/L)) or urine M-protein (ie, < 200 mg (0.2 g) per 24 hours) and with measurable involved sFLC are considered oligosecretory and must have sFLC assessed at each cycle until confirmed progression. Please note that SPEP and UPEP should still be followed in those patients.
   b. In subjects with measurable disease in serum &/or urine, sFLC must be assessed a time of serum and urine IFE negativity to assess for sCR
3) **Urine**: 24-hour urine collection for M protein quantification and immunofixation. 24-hour urine must be collected with each cycle for all subjects.

a. Urine Immunofixation (IFE) is required at baseline and to confirm CR, regardless of whether measurable M-protein was present at baseline.
b. Subjects with measurable disease in UPEP will be assessed for response based on UPEP and not by the serum FLC assay.
c. Subjects with measurable disease in both SPEP and UPEP will be assessed for response based on these two tests and not by the serum FLC assay
d. Subjects with FLC only disease (i.e. serum and urine IFE negative) should be monitored by sFLC only; SPEP, UPEP and IFE are required only to code CR in those subjects
e. Subjects with measurable disease by sFLC only, but with non-measurable urine M-protein, will be monitored by sFLC assay for response. However, their UPEP should also be monitored for progression.

4) **Bone marrow aspirate**:

Bone marrow aspirate samples will be collected at the timepoints described below for the [redacted] disease assessment (% plasma cells and light chain restriction)[redacted].

Disease assessments for CR/sCR confirmation will be performed at the local lab. These include but are not limited to plasma cell percentage and light chain restriction, per IMWG criteria (See Appendix 3).

[redacted] bone marrow aspirate samples should be collected at the following timepoints:

- Required collections at: Screening, ≥VGPR, and every 6 cycles thereafter until PD. In subjects with confirmed PD, bone marrow aspirate collection is optional.

[redacted]

Table 5.4.2-1: Bone Marrow Aspirate Samples			
Collection	**Timing**	**Local Laboratory**	**Central Laboratory**
Required	• Screening (within 35 days of randomization)	• Plasma Cell Percentage (PC %)	• FISH (at screening only) • [redacted] • [redacted]
Required	• ≥VGPR, then every 6 cycles thereafter until PD. • Bone marrow aspirate is optional upon progression confirmation.	• PC %, • Light chain restriction *N.B. Only required to confirm CR and sCR.*	• [redacted] • [redacted]
[redacted]			

Note: Bone marrow biopsy is not required by protocol unless an aspirate sample (at any time point above) is not available due to a dry tap. In cases of dry tap, bone marrow biopsy can only be used for assessment of PC% and Kappa/lambda ratio by IHC

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

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

5.4.3 Imaging Assessments for Myeloma

5.4.3.1 Skeletal Survey

Skeletal survey, by conventional radiography, for metastatic disease will be performed within 28 days of randomization in all subjects. Skeletal survey will be performed on study if clinically indicated (development of compression fracture does not exclude response). Use of conventional or low dose CT scan (ie, of the spine) or 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. The number and location of skeletal lesions and whether they are lytic should be recorded on the eCRF. On treatment survey should record whether there is an increase in the number or size of lytic lesions.

5.4.3.2 Assessment of Extramedullary Plasmacytoma

Computed tomography or MRI should be performed at screening, if clinically indicated or if patient had a previous extramedullary or bone plasmacytoma. To minimize unnecessary radiation in myeloma subjects where progression is primarily based on serum and urine M-protein, on study assessments should only be performed if clinically indicated (ie, pain, concern for disease

progression), whether or not present at baseline. In subjects with baseline plasmacytoma, imaging follow-up should be done regularly per investigator's discretion. Imaging confirmation of disappearance of plasmacytoma is required at time of CR/sCR if it was not confirmed before.

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

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

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.

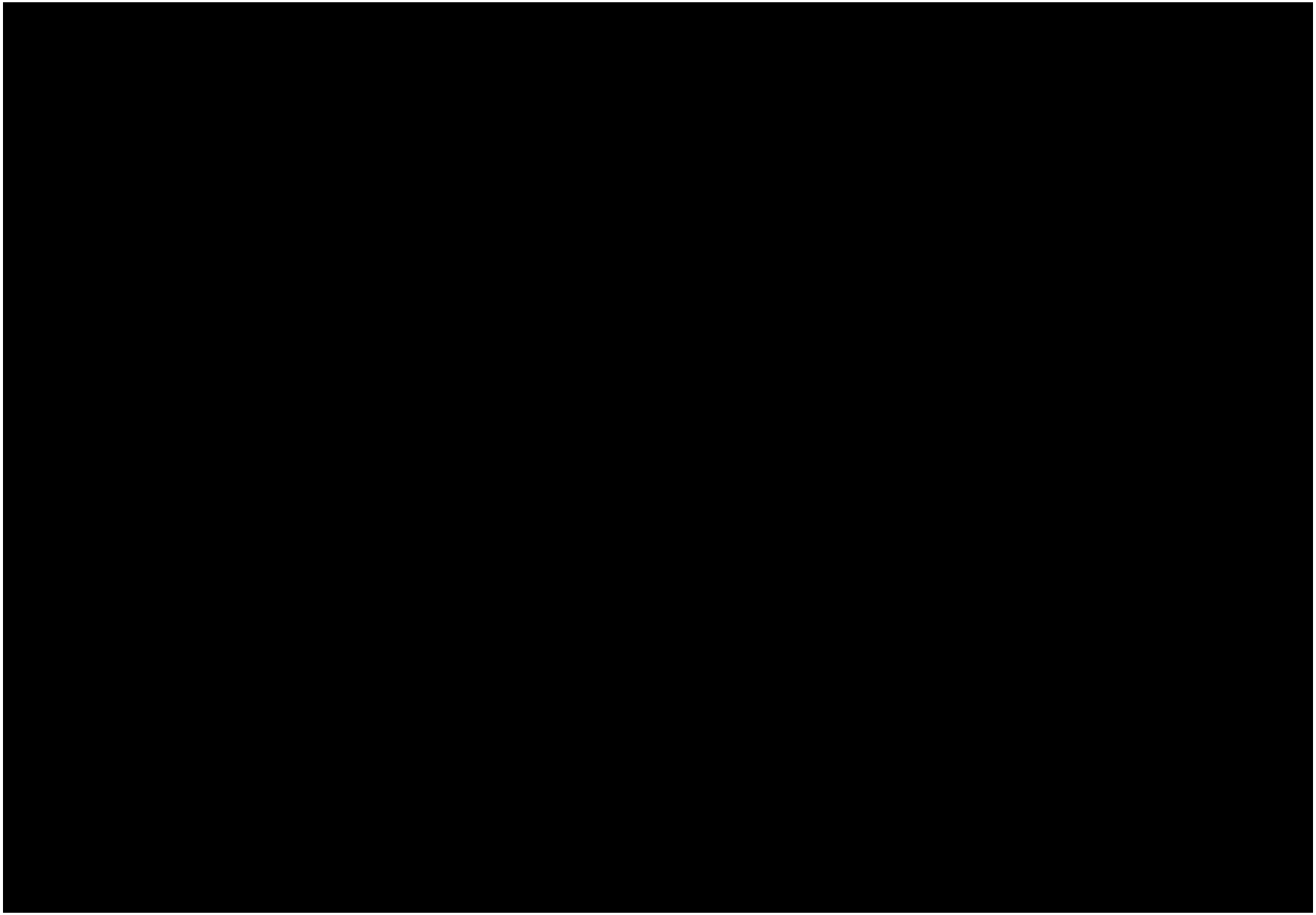
Non-measurable disease are all other lesions (or sites of disease), including those that are too small (ie, do not meet above criteria), occur within a previously irradiated area (unless they are documented as new lesions since the completion of radiation therapy), bone lesions, leptomeningeal disease, 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.

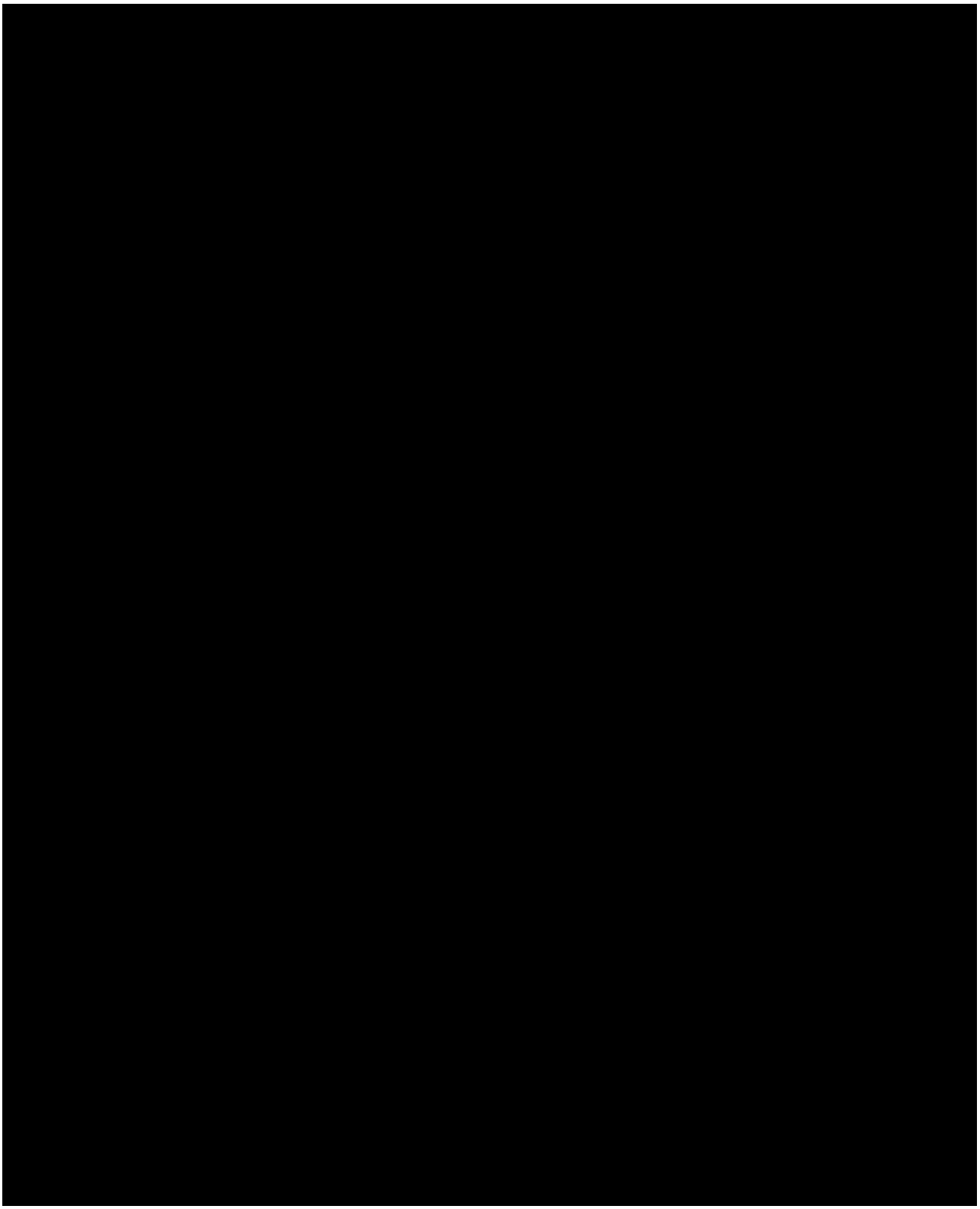
5.4.4 Definitions of Response and Progression Criteria

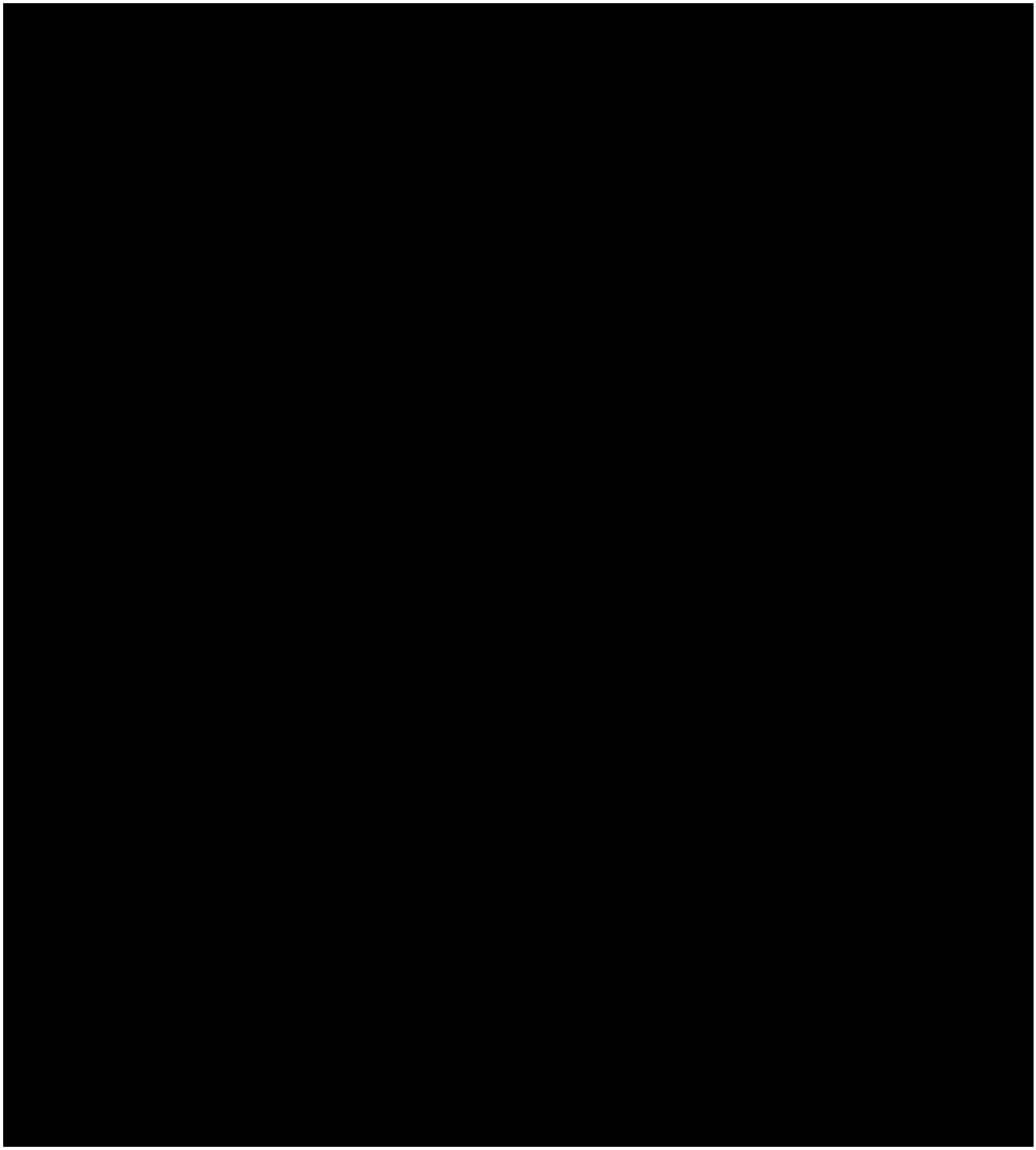
See Appendix 3 for definitions of response and progression. All criteria are derived from IMWG[32,33,34]. All response and progression categories require 2 consecutive assessments to confirm response and progression before initiation of any new therapy.

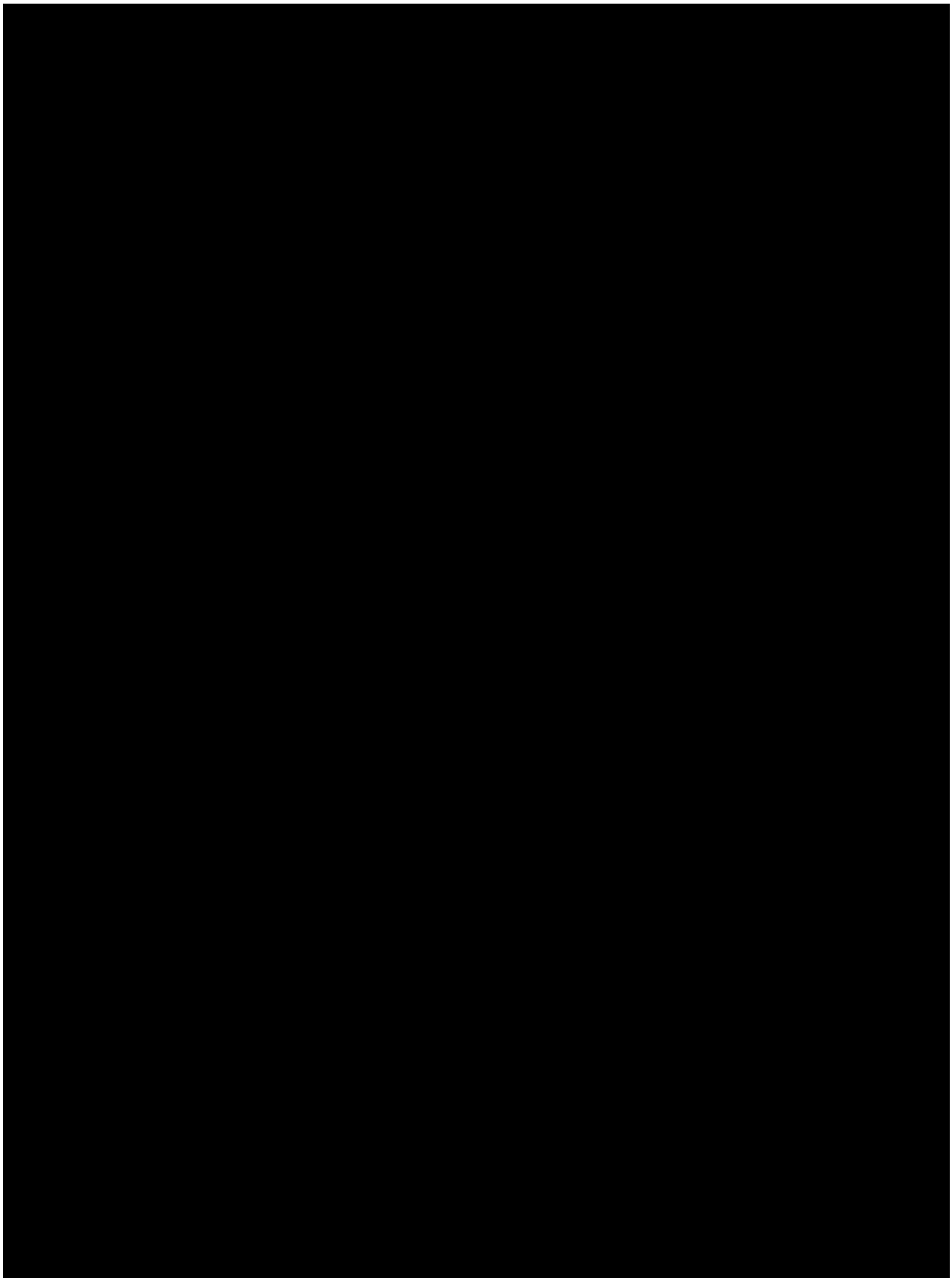
NB: Table in Appendix 3 is inclusive of multiple response category definitions; however, the protocol/CRF is not reporting on all of these response categories.

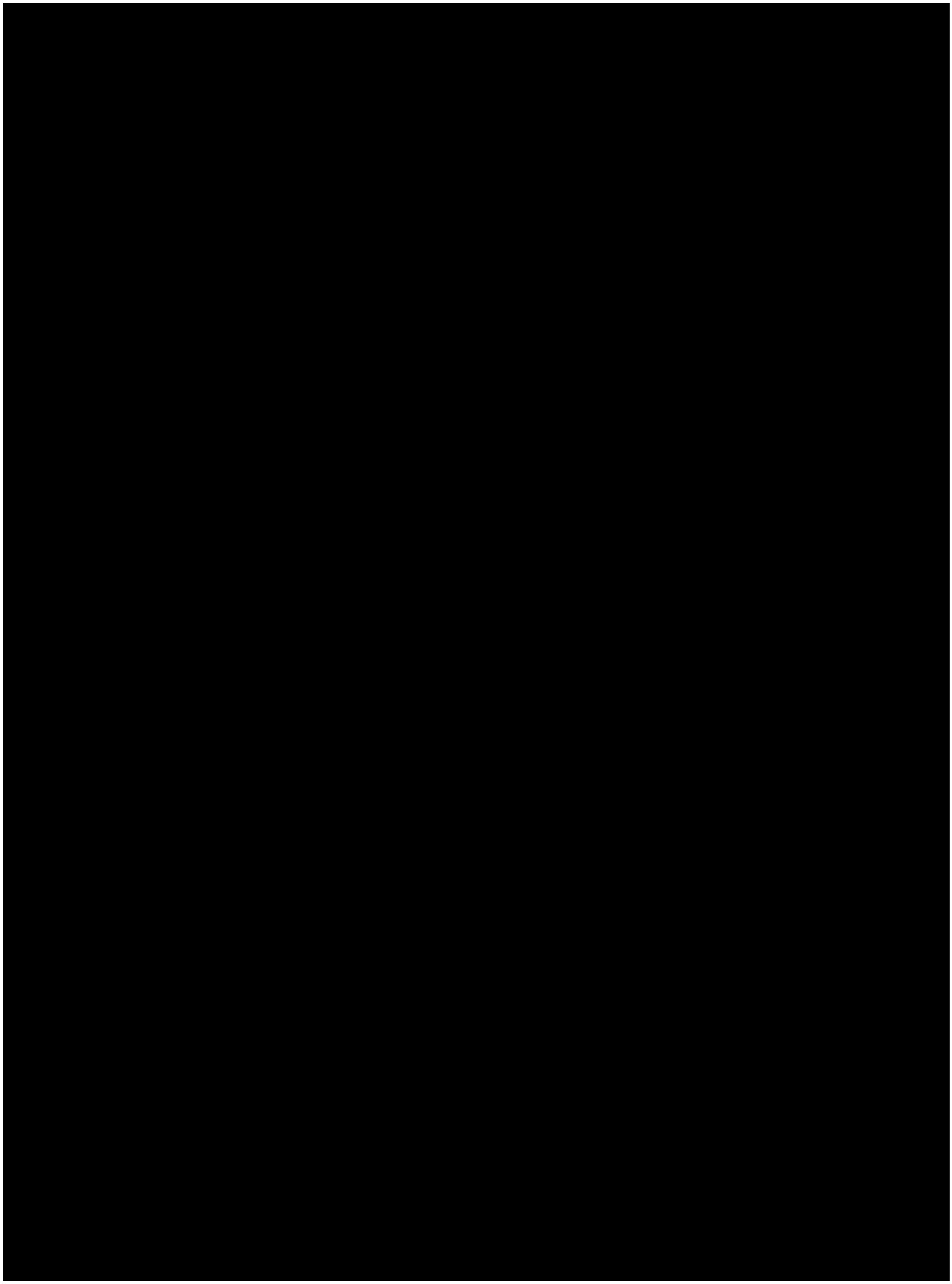
[redacted]











5.8 Other Assessments

Not applicable

5.9 Results of Central Assessments

All efficacy laboratory assessments should be performed by the central laboratory. Investigative site staff will receive reports of the results on an ongoing basis for treatment decisions and patient management throughout the study. If the investigator chooses to perform any additional serum and urine myeloma lab tests locally, the results must be reported in the CRF.

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.)

BMS will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320.

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 of the nivolumab and elotuzumab Investigator Brochure (IB) contains 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 or within 30 days of the last visit for screen failures. For subjects randomized and never treated with study drug, SAEs should be collected for 30 days from the date of randomization.

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

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.

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

6.2 Nonserious Adverse Events

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

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug until 100 days from the last dose of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

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

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

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form electronic) as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

- 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 study subject is pregnant or may have been pregnant at the time of study exposure, including during at least time to washout plus one ovulatory cycle (30 days) for a total of 23 weeks, or plus one spermatogenesis cycle (90 days) for a total of 31 weeks after product administration (for patients in arms A and C; 4 week duration needed for arm B), the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1. Refer to pomalidomide pregnancy risk prevention plan for additional information (Appendix 6).

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

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.).

Of note, doses up to 20mg/kg of elotuzumab and doses of up to 10mg/kg of nivolumab have been safely administered in prior studies.

6.6 Potential Drug Induced Liver Injury (DILI)

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

Potential drug induced liver injury is defined as:

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

   AND

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

   AND

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

6.7 Other Safety Considerations

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

Second primary malignancies (SPMs) will be collected throughout the study which includes assessments during survival follow-up. All SPMs that occur during the screening period and within 60 days of discontinuation of dosing will be reported as an SAE regardless of relationship to study drug. Additionally, any SPM that occurs after this timeframe and considered related to study drug will be reported as an SAE. All other SPMs will be collected and reported on a separate CRF page.

Immune-mediated adverse events (IMAEs) are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. IMAEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the subject's case report form.

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

An independent data monitoring committee (DMC) will be established before the first subject is

treated to provide oversight of safety and study conduct. The DMC will review safety and efficacy data at periodic intervals.

The first comprehensive safety review will occur after the first 42 treated subjects (ie, the first 6 subjects in the exploratory arm) have been followed for 1 month

An independent review committee (IRC) had been set up to review blinded responses and progression criteria in each subject. However, after enrollment was discontinued, it was decided to discontinue efficacy assessment by IRC.

Separate charters will provide further guidance and describe the activities of these committees.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

Prior to Revised Protocol 02, the study planned to randomize 406 subjects at a 3:3:1 ratio to N-Pd vs Pd vs NE-Pd. Also, subjects randomized to the Pd control arm were allowed to cross-over to the exploratory NE-Pd arm upon progression. As of 1 September 2017, cross-over was no longer permitted and as of Revised Protocol 02, the exploratory NE-Pd arm was closed to enrollment.

In Revised Protocol 02, the planned sample size for this study was revised to approximately 348 randomized subjects randomized at a 1:1 ratio to N-Pd vs Pd. The sample size of the study accounts for the primary efficacy endpoint of PFS. PFS will be evaluated for treatment effect at the overall alpha level of 0.05 (two-sided) with 90% power with two interim analyses, with the first one for early futility and the second for efficacy.

- The study requires at least 262 PFS events to ensure that a two-sided 5% type I error sequential test procedure with two interim analyses will have 90% power to detect a hazard ratio (HR) of 0.667, corresponding to a median PFS of 6 vs 4 months for the N-Pd and Pd arms, respectively.

East version 6.3 was used for sample size/power computation.

Table 8.1-1: Schedule of Analyses

	Interim analysis for PFS	Final analysis for PFS
Condition for PFS	Interim 1: at least 131 PFS events (for futility only) Interim 2: at least 184 PFS events (for efficacy only)	at least 262 PFS events
Expected timing	Interim 1: 8 months after enrollment is reopened Interim 2: 16 months after enrollment is re-opened	22 months after enrollment is re-opened

Table 8.1-1: Schedule of Analyses

	Interim analysis for PFS	Final analysis for PFS
Alpha Level	Interim 1: Futility boundary on HR 1.053 Interim 2: PFS at 0.0148 level[a]	Final PFS at 0.0456 level[a]

[a] Using Lan-DeMets α spending function with O'Brien and Fleming type of boundary when exactly 184 PFS events are observed at the interim analysis for PFS.

On 23-August-2018, the Sponsor (BMS) decided to permanently discontinue enrollment based on insufficient clinical benefit observed at an interim futility analysis for PFS. A total of 170 subjects had been randomized in the study.

8.2 Populations for Analyses

- All Enrolled subjects: All subjects who signed an informed consent form and were registered into the IWRS
- All Randomized subjects: All enrolled subjects who were randomized to any treatment arm. This is the primary dataset for analyses of study conduct, efficacy parameters, baseline characteristics [redacted]
- All Treated subjects: All randomized subjects who received at least one dose of study drug. This is the primary dataset for safety and exposure analyses.

[redacted]

8.3 Endpoints

8.3.1 Primary Endpoint

The primary objectives in the study will be measured by the primary endpoint of PFS assessed by investigator within the N-Pd and Pd arms.

8.3.1.1 Progression Free Survival

PFS is defined as the time from randomization to the date of the first documented tumor progression or death due to any cause. PFS will be determined by an investigator, based upon laboratory data (eg, SPEP/IFE, UPEP/IFE, bone marrow disease assessment, serum FLC) as defined by the IMWG criteria. Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last efficacy assessment. Subjects who did not have any on study efficacy assessments and did not die will be censored on the date they were randomized. Subjects who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last efficacy assessment prior to subsequent anti-cancer therapy.

8.3.2 Secondary Endpoint(s)

Overall Survival (OS)

OS is defined as the time between the date of randomization and the date of death due to any cause. OS will be censored on the last date a subject was known to be alive.

Objective Response Rate (ORR)

Objective response rate is defined as the proportion of randomized subjects who achieve a best overall response of stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR) using the IMWG criteria.

Time to Response (TTR)

Time to Response (TTR) is defined as the time from the date of randomization to the date of the first sCR, CR, VGPR, or PR. TTR will be evaluated for responders (BOR is either sCR, CR, VGPR, or PR) only.

Duration of Response (DOR)

Duration of Response (DOR) is defined as the time between the date of first response to the date of the first objectively documented tumor progression as assessed by independent review committee according to modified IMWG criteria or death due to any cause prior to subsequent anti-cancer therapy. Subjects who neither progress nor die will be censored on the date of their last tumor assessment prior to subsequent anti-cancer therapy. DOR will be evaluated for responders (BOR is either sCR, CR, VGPR, or PR) only.

8.3.3 Exploratory Endpoint(s)

Within the NE-Pd arm, the following endpoints are considered as exploratory endpoints, ORR, PFS, DOR, and TTR by investigator.

For subjects who crossed-over from the control arm (Pd) to the exploratory arm (NE-Pd), the following endpoints are considered as exploratory efficacy endpoints, ORR, PFS, DOR, and TTR by investigator.

[redacted]

8.4 Analyses

The main analysis will be performed after the last subject has complete safety follow up (at least 100 days after study drug discontinuation).

8.4.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized for all randomized subjects by treatment group, as randomized, using descriptive statistics.

8.4.2 Efficacy Analyses

8.4.2.1 Methods for Primary Endpoints

PFS Analysis Time points

- At the time of PFS analyses, as assessed by investigator, the distribution of PFS in N-Pd group will be compared with the Pd via a two-sided, log-rank test stratified by prior lines of therapy and ISS stage at study entry. The hazard ratio (HR) and the corresponding 100x(1-adjusted alpha)% confidence interval (CI) will be estimated in a stratified Cox proportional hazards model using treatment as a single covariate.
- PFS curves, PFS medians with two-sided 95% CIs, and PFS rates at select milestone with 95% CIs will be estimated using Kaplan-Meier methodology.

8.4.2.2 Methods for Secondary Endpoints

Analysis of OS

- At the time of PFS analyses, OS will be summarized by the Kaplan-Meier product-limit method within each arm. Median values along with two-sided 95% CIs based on the log-log transformation, will be calculated. Additional details of OS analysis will be included in the SAP

Analysis of ORR by Investigator

- Investigator-determined ORR analyses will be conducted using a two-sided Cochran-Mantel-Haenszel (CMH) test stratified by prior lines of therapy and ISS stage at study entry to compare N-Pd to Pd arm. Associated odds ratios and 95% CIs will be calculated. Additionally, ORRs and corresponding 95% exact CIs will be calculated using the Clopper-Pearson method for N-Pd and Pd arms

Analysis of DOR and TTR

- DOR and TTR will be computed for subjects who achieve sCR, CR, VGPR, or PR as assessed by investigator according to modified IMWG criteria. Median values of DOR, along with two-sided 95% CI, will be calculated using KM product-limit method. Summary statistics of TTR will be provided. More detailed analysis of DOR and TTR will be described in the SAP

Details on the testing procedure will be described in SAP.

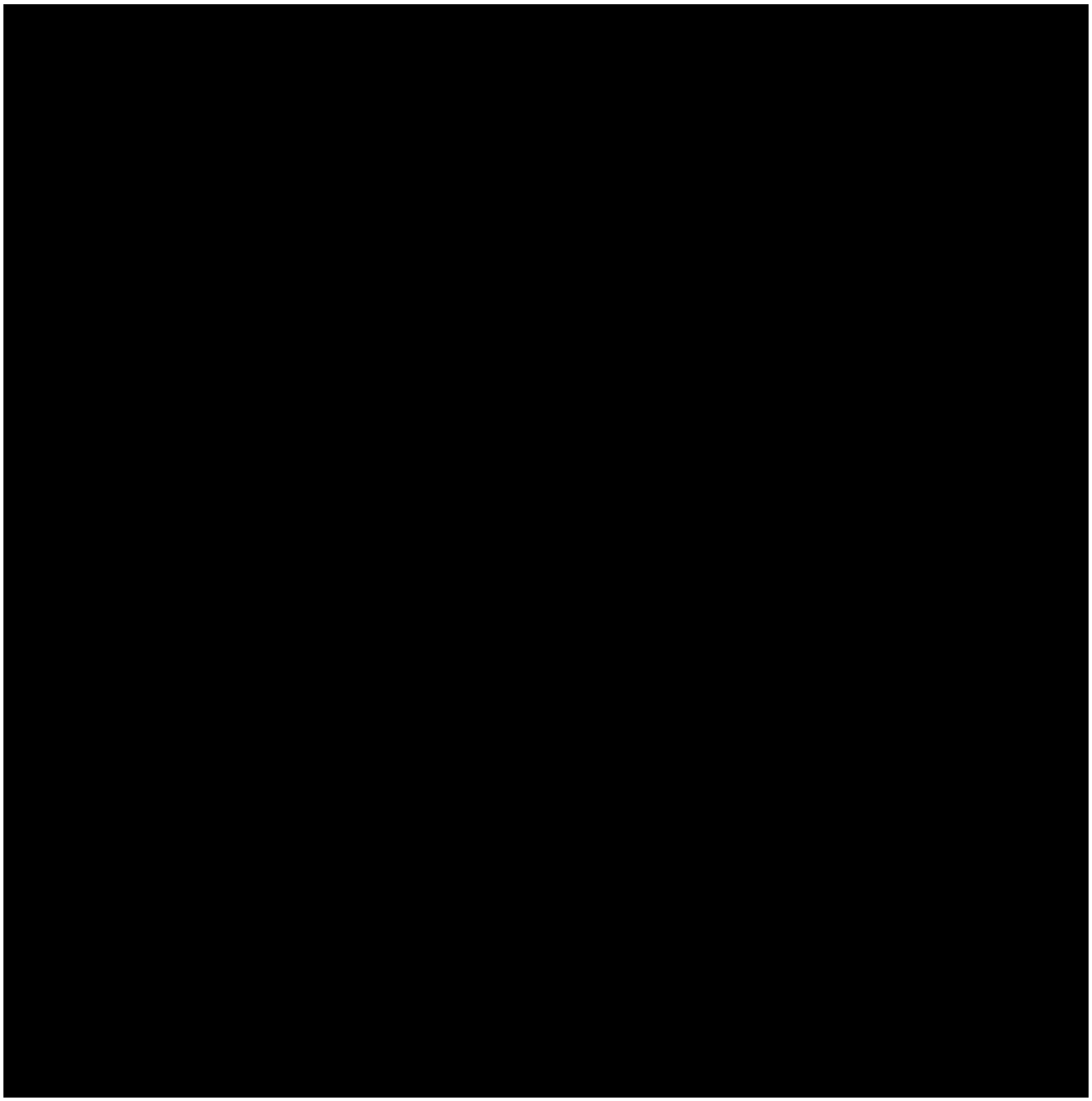
8.4.2.3 Methods for Exploratory Endpoints

Details of following analyses will be included in the SAP.

- Analyses of the data for subjects who crossed-over from the control arm (Pd) to the exploratory arm (NE-Pd) will be analyzed separately
- Analyses of the data in NE-Pd arm are of exploratory nature and may be performed at several times prior to completion of the study in order to facilitate program decisions

8.4.3 Safety Analyses

The safety analysis will be performed in all treated subjects. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 by treatment group. Adverse Events (AE), drug-related AEs, Serious Adverse Events (SAE) and drug-related SAEs will be tabulated using worst grade per NCI CTCAE v.4.0 criteria by system organ class and preferred term. On-study lab parameters including hematology, chemistry, liver function and renal function will be summarized using worst grade per NCI CTCAE v.4.0 criteria.



8.4.7 Other Analyses

Not applicable

8.5 Interim Analyses

Interim Analysis for PFS Futility

At FDA's request on 21-June-2018, a formal PFS interim analysis for futility was conducted in August 2018 based on the database lock on 12-April-2018. The investigator assessed progression events (NPd and Pd arms) were used in this analysis. Prior to running the futility analysis, a futility criteria was defined based on conditional power assuming 85 events (30% information fraction). The stopping criteria for futility was that the conditional power under observed trend is strictly less than 1%. This would correspond to a HR (NPd vs. Pd) boundary of 0.995 and the corresponding conditional power under alternative would be 67.8%, ie if alternative hypothesis is true (HR = 0.667), there is still 67.8% chance that the study will be positive at the final analysis.

Subsequently, after conducting the interim analysis, the decision was made to permanently discontinue enrolment based on insufficient clinical benefit observed at an interim futility analysis for PFS. All futility analyses were conducted by the unblinded independent statistics vendor.

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. CRF pages and/or electronic files may serve as the source documents: such as outcome assessments.

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

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

9.1.2.1 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 CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

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

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

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

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of study drug (inventoried and dispensed) is maintained at the study site for 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 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. CRFs 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 CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

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

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

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

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

9.3 Clinical Study Report and Publications

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

For this protocol, the Signatory Investigator will be selected as appropriate based on the following criteria:

- Involvement in trial design
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study 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

N/A

11 LIST OF ABBREVIATIONS

Term	Definition
[redacted]	
ADCC	Antibody dependent cell-mediated cytotoxicity
AE	Adverse event
BMS	Bristol-Myers Squibb
CDR	Complementary Determining Regions
°C	Celsius
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CMMC	Circulating Multiple Myeloma Cells
CR	Complete response
CRF	Case Report Form
CrCl	Creatinine Clearance
CS1	CD-2 subset 1
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DILI	Drug induced liver injury
DLT	Dose-limiting toxicity
DMC	Data monitoring committee
DVT	Deep Vein Thrombosis
EBMT	European Group for Blood and Bone Marrow Transplant
ECG	Electrocardiogram
[redacted]	
E-Pd	Elotuzumab Pomalidomide (low dose) dexamethasone
EPO	Erythropoietin
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
HCG	Human Chorionic Gonadotropin
HR	Hazard Ratio

Term	Definition
[redacted]	
HRT	Hormone replacement therapy
ICH	International Council on Harmonization
IF	Immunofixation
IHC	Immunohistochemistry
I-O	Immuno-oncology
IL-2	Interleukin 2
IMiDs	Immune Modulatory Drugs
IMWG	International Myeloma Working Group
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IRC	Independent Review Committee
IV	Intravenous
ITT	Intent-to-treat
NE-Pd	Nivolumab Elotuzumab Pomalidomide dexamethasone
NK	Natural Killer
NKT	Natural Killer T-Cells
N-Pd	Nivolumab pomalidomide dexamethasone
Ld	Lenalidomide (low-dose) dexamethasone
LD	Lenalidomide (high-dose) dexamethasone
LdE	Lenalidomide, (low-dose) dexamethasone, elotuzumab
LPFV	Last patient first visit
[redacted]	
MGUS	Monoclonal Gammopathy of Undetermined Significance
MM	Multiple Myeloma
MR	Minor (Minimal) Response
[redacted]	
MRI	Magnetic Resonance Imaging
MTD	Maximum tolerated dose
NK	Natural Killer
NKT	Natural Killer T-cell

Term	Definition
ORR	Objective Response Rate
OS	Overall Survival
Pd	Pomalidomide (low dose) dexamethsone
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial Response
[redacted]	
rrMM	relapsed refractory Multiple Myeloma
SAE	Serious adverse event
sCR	Stringent complete response
sMICA	soluble major histocompatibility complex class I chain-related gene A
SLAMF7	Signaling Lymphocyte Activation Molecule family 7
SPM	Second primary malignancy
[redacted]	
SMM	Smoldering Multiple Myeloma
WOCBP	Women of childbearing potential
VGPR	Very Good Partial Response

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APPENDIX 1 DEFINITION OF LINES OF THERAPY

Line of Therapy (from International Myeloma Working Group (Rajkumar, 2011)) is defined 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 autologous stem cell transplantation, followed by maintenance is considered one line of therapy. Each subsequent 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 ECOG PERFORMANCE STATUS

These scales are used by doctors and researchers to assess how a patient's disease progressing, assess how the disease affects the dailing living abilitiesof the patient and determine appropriate treatment and prognosis. They are included here for health care professionsals to assess.

ECOG PERFORMANCE STATUS	
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Toxicity and Response Criteria of the Eastern Cooperative Oncology Group.

APPENDIX 3 DEFINITIONS OF RESPONSE AND PROGRESSION CRITERIA

NB: The table below is inclusive of multiple response category definitions; however, the protocol/CRF is not reporting on all of these response categories. The standard IMWG response criteria have been limited to the eligible patient population in the study.

Table 1: IMWG criteria for response assessment including criteria for minimal residual disease

Response Subcategory	Response criteria[a]
IMWG MRD criteria (requires a complete response as defined below)	
Sustained MRD-negative	MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years)[b]
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher[1]
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Imaging-positive MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue[c]
Standard IMWG response criteria	
Stringent complete response	Complete response as defined below plus normal FLC ratio and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤ 4:1 or ≥ 1:2 for κ and λ patients, respectively, after counting ≥ 100 plasma cells)[d]
Complete response[e]	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow aspirates
Very good partial response[e]	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg per 24 h
Partial response	≥ 50% reduction of serum M-protein plus reduction in 24 h urinary M-protein by ≥ 90% or to < 200 mg per 24 h; If the 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; If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥ 30%. In addition to these criteria, if present at baseline, a ≥ 50% reduction in the size (SPD)[f] of soft tissue

Table 1: IMWG criteria for response assessment including criteria for minimal residual disease

	plasmacytomas is also required
Minimal response	≥ 25% but ≤ 49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50–89%. In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size (SPD)[f] of soft tissue plasmacytomas is also required
Stable disease	Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease
Progressive disease[g]	Any one or more of the following criteria: 1. Increase of 25% from lowest confirmed response value in one or more of the following criteria: a) Serum M-protein (absolute increase must be ≥ 0.5 g/dL); b) Serum M-protein increase ≥ 1 g/dL, if the lowest M component was ≥ 5 g/dL; c) Urine M-protein (absolute increase must be ≥ 200 mg/24 h); d) 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); 2. Appearance of a new lesion(s), ≥ 50% increase from nadir in SPD[f] of > 1 lesion, or ≥ 50% increase in the longest diameter of a previous lesion > 1 cm in short axis;

IMWG=International Myeloma Working Group. MRD=minimal residual disease. NGF=next-generation flow. NGS=next-generation sequencing. FLC=free light chain. M-protein=myeloma protein. SPD=sum of the products of the maximal perpendicular diameters of measured lesions. FCM=flow cytometry. SUV_{max}=maximum standardised uptake value. MFC=multiparameter flow cytometry. ^{18}F-FDG PET=^{18}F -fluorodeoxyglucose PET.

[a] **All response categories require two consecutive assessments made any time before starting any new therapy**; for MRD there is no need for two consecutive assessments, but information on MRD after each treatment stage is recommended (eg, after induction, high-dose therapy/ASCT, consolidation, maintenance). MRD tests should be initiated only at the time of suspected complete response. All categories of response and MRD require no known evidence of progressive or new bone lesions if radiographic studies were performed. However, radiographic studies are not required to satisfy these response requirements except for the requirement of FDG PET if imaging MRD-negative status is reported. Each category, except for stable disease, will be considered unconfirmed until the confirmatory test is performed. The date of the initial test is considered as the date of response for evaluation of time dependent outcomes such as duration of response.

[b] Sustained MRD negativity when reported should also annotate the method used (eg, sustained flow MRD-negative, sustained sequencing MRD-negative).

[c] Criteria used by Zamagni and colleagues,[2] and expert panel (IMPetUs; Italian Myeloma criteria for PET Use).[3, 4] Baseline positive lesions were identified by presence of focal areas of increased uptake within bones, with or without any underlying lesion identified by CT and present on at least two consecutive slices. Alternatively, an SUVmax=2·5 within osteolytic CT areas >1 cm in size, or SUVmax=1·5 within osteolytic CT areas ≤ 1 cm in size were considered positive. Imaging should be performed once MRD negativity is determined by MFC or NGS.

[d] Presence/absence of clonal cells on immunohistochemistry is based upon the κ/λ/L ratio. An abnormal κ/λ ratio by immunohistochemistry 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.

[e] When the only method to measure disease is by serum FLC levels: complete response can be defined as a normal FLC ratio of 0·26 to 1·65 in addition to the complete response criteria listed previously. Very good partial response in such patients requires a ≥ 90% decrease in the difference between involved and uninvolved FLC levels

[f] Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumour size will be determined by the SPD

[g] Positive immunofixation alone in a patient previously classified as achieving a complete response will not be considered progression. In the case where a value is felt to be a spurious result per physician discretion (eg, a possible laboratory error), that value will not be considered when determining the lowest value.

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APPENDIX 4 THE INTERNATIONAL STAGING SYSTEM (ISS) FOR MULTIPLE MYELOMA

Stage	Criteria	Median Survival (months)
Stage I	Serum β2-microglobulin < 3.5 mg/L (296.2 nmol/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 (296.2 nmol/L) but serum albumin < 3.5 g/dL OR β2-microglobulin 3.5 to < 5.5 mg/L (296.2 to < 465.5 nmol/L) irrespective of the serum albumin level	44
Stage III	Serum β2-microglobulin ≥ 5.5 mg/L (465.5 nmol/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 5 NIVOLUMAB MANAGEMENT ALGORITHMS

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

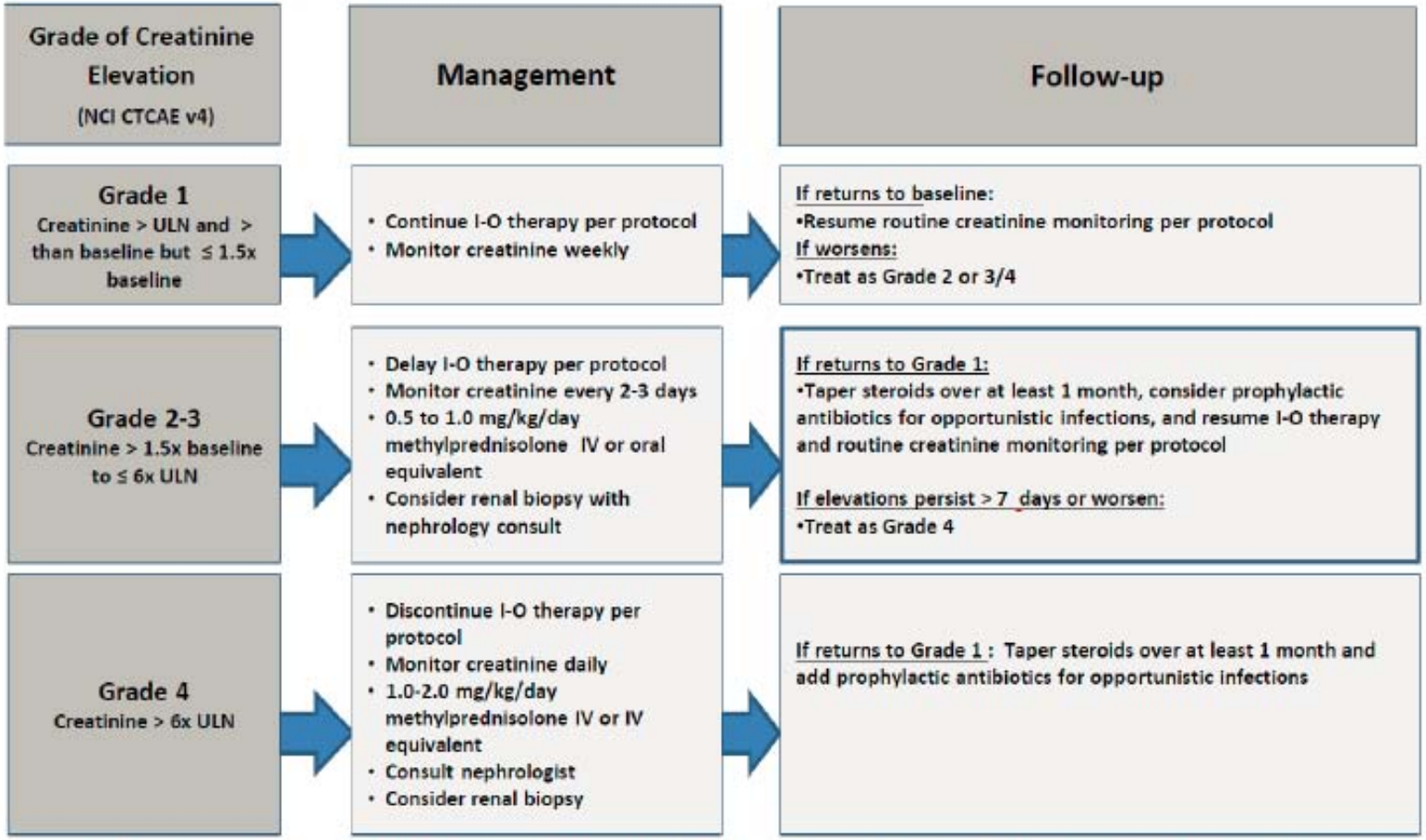
Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

27-Jun-2018

Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

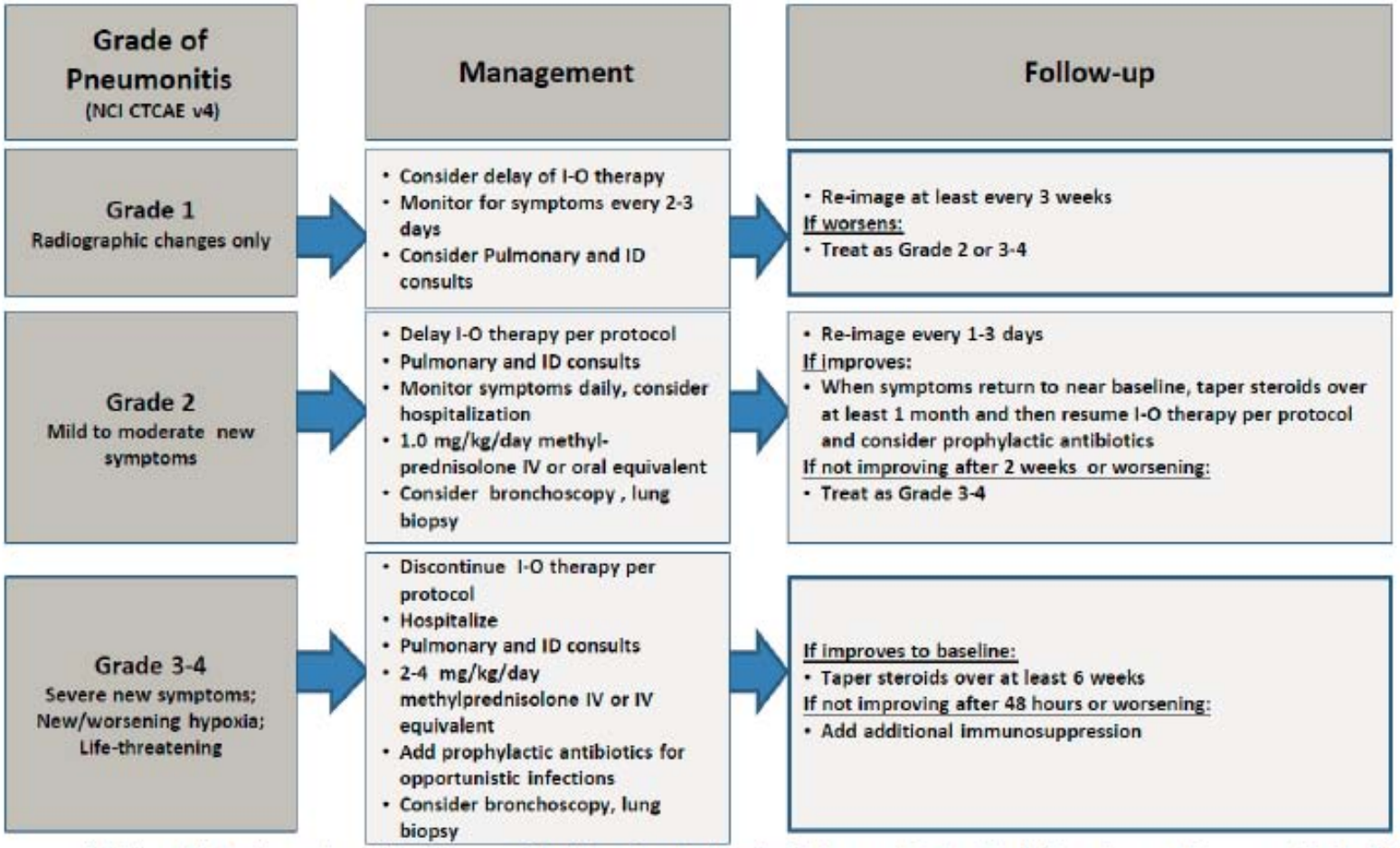


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

27-Jun-2018

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

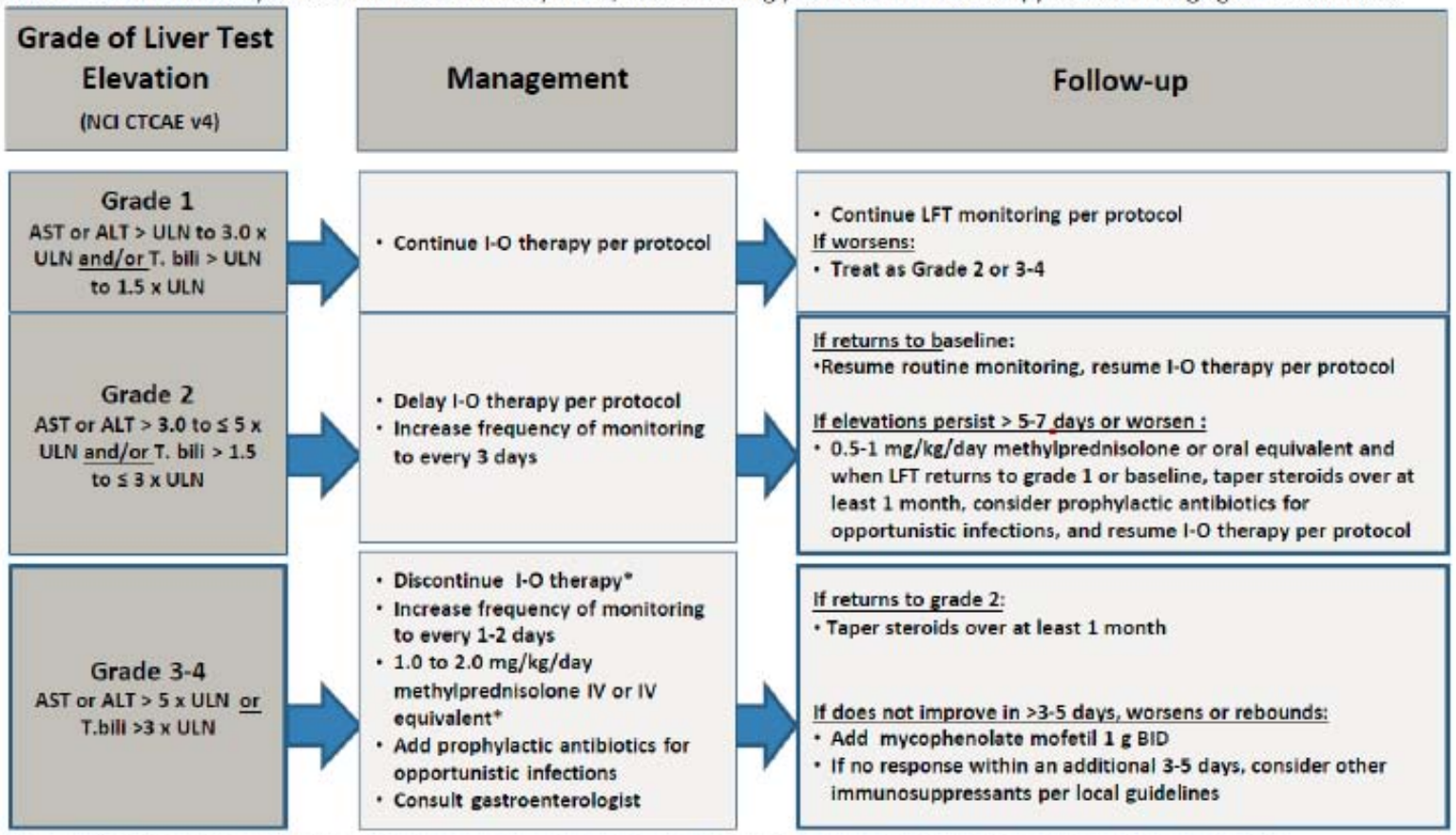


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids

27-Jun-2018

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.



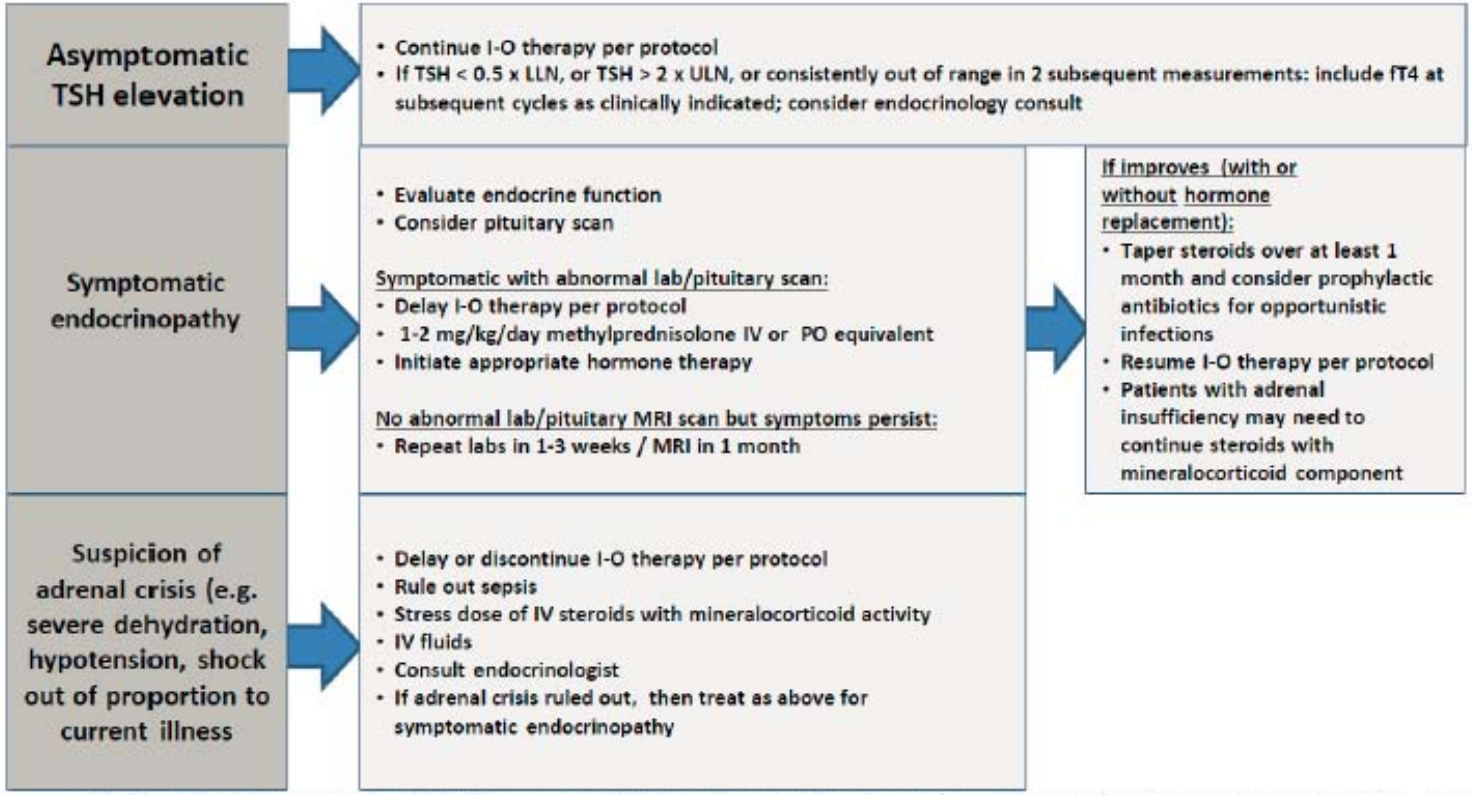
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

27-Jun-2018

Endocrinopathy Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.

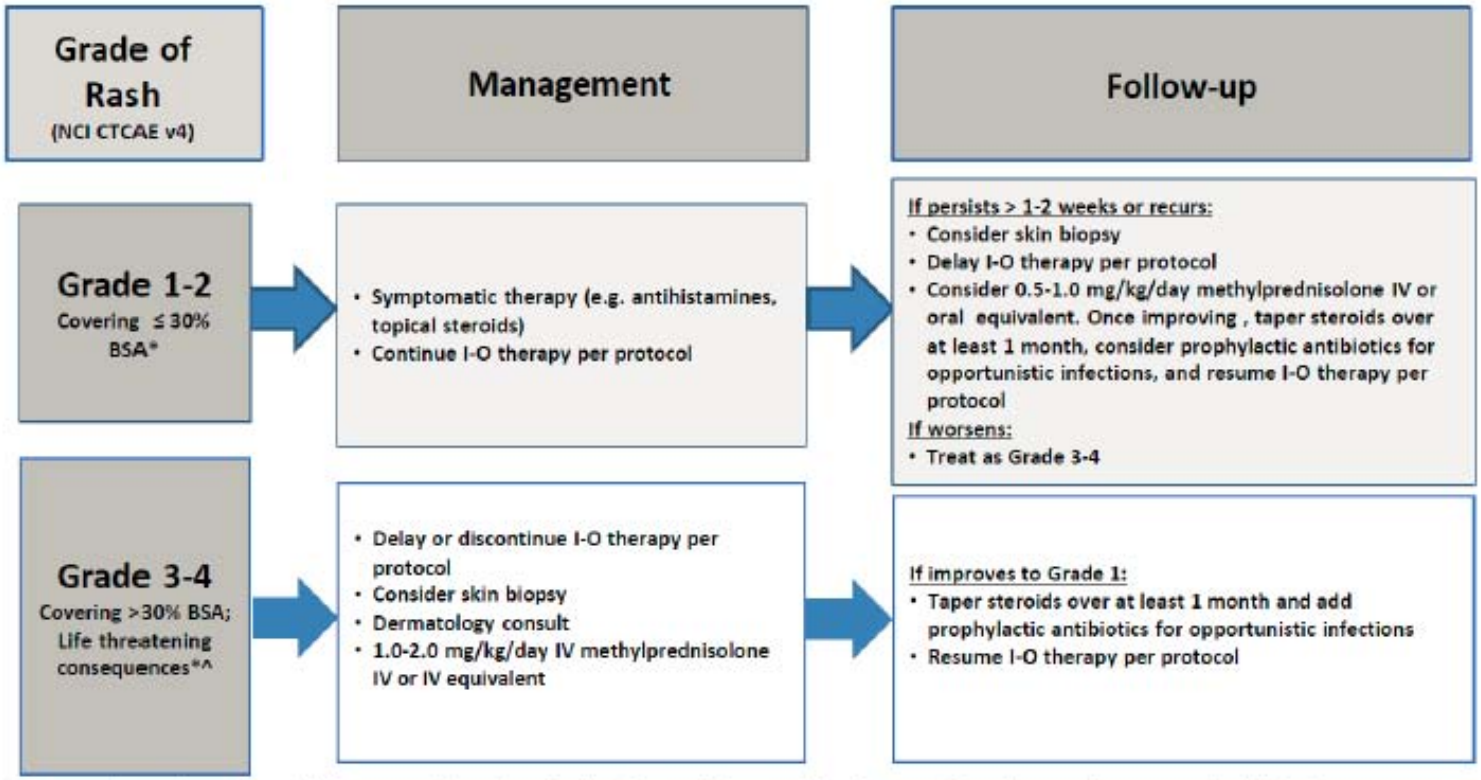


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

27-Jun-2018

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

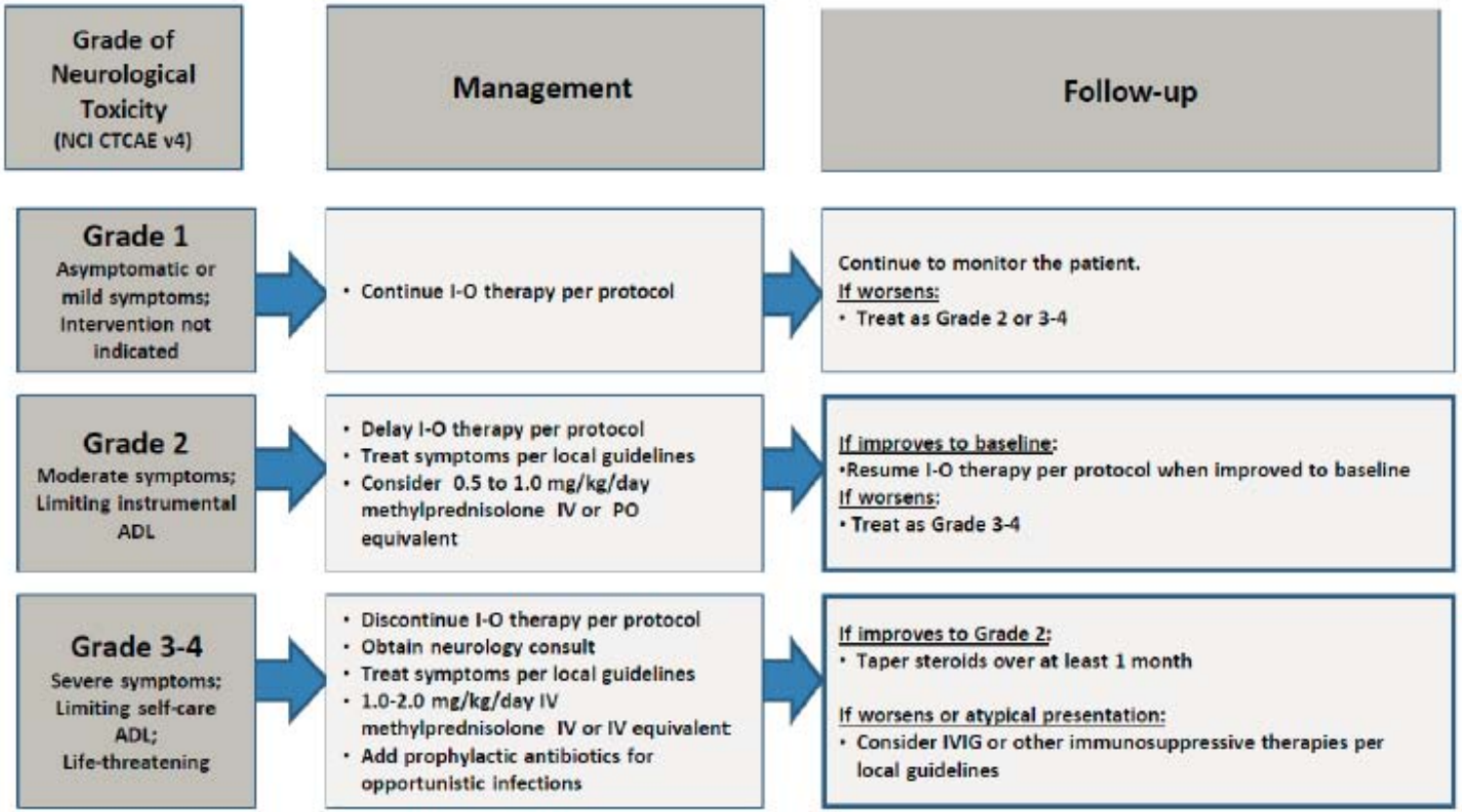
*Refer to NCI CTCAE v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

27-Jun-2018

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

27-Jun-2018

APPENDIX 6 POMALIDOMIDE PREGNANCY RISK PREVENTION PLAN

Appendix 6 only applies to participants in certain countries or regions.

All participants must follow either the local pomalidomide risk management program or the Pomalidomide Pregnancy Risk Prevention Plan.

1 POMALIDOMIDE PREGNANCY PREVENTION PLAN FOR SUBJECTS IN CLINICAL TRIALS

The Pregnancy Prevention Plan (PPP) applies to all subjects receiving pomalidomide within a clinical trial. The following PPP documents are included:

1. The Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods document (Section 2) provides the following information:
   - Potential risks to the fetus associated with pomalidomide exposure
   - Definition of Female of Childbearing Potential (FCBP) / female not of childbearing potential (FNCBP)
   - Requirements for counseling of all subjects receiving pomalidomide about pregnancy precautions and the potential risks of fetal exposure to pomalidomide
   - Acceptable birth control methods for both female subjects of childbearing potential and male subjects receiving pomalidomide in the study
   - Pregnancy testing requirements for subjects receiving pomalidomide who are FCBP
2. The Pomalidomide Education and Counseling Guidance Document for each gender (female and male (Section 3 and Section 4 respectively) must be completed and signed by a trained counselor at the participating clinical center prior to each dispensing of pomalidomide. A copy of this document must be maintained in the subject's records for each dispense.
3. The Pomalidomide Information Sheet (Section 4) will be given to each subject receiving pomalidomide. The subject must read this document prior to starting pomalidomide and each time the subject receives a new supply of pomalidomide.

2 POMALIDOMIDE RISKS OF FETAL EXPOSURE, PREGNANCY TESTING GUIDELINES AND ACCEPTABLE BIRTH CONTROL METHODS

2.1 Risks Associated with Pregnancy

Pomalidomide was teratogenic in both rats and rabbits when administered during the period of organogenesis. 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 can cause birth defects or death to an unborn baby.

The teratogenic effect of pomalidomide in humans cannot be ruled out. Therefore, a pregnancy prevention program must be followed.

2.1.1 Definition of Females of Childbearing Potential (FCBP)

A FCBP is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) 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).

2.1.2 Definition of Females Not of Childbearing Potential

Females who do not meet the above definition of FCBP should be classified as FNCBP.

2.2 Counseling

2.2.1 Females of Childbearing Potential

For a FCBP, pomalidomide is contraindicated unless all of the following are met (ie, all FCBP must be counseled concerning the following risks and requirements prior to the start of pomalidomide):

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 28 days before starting pomalidomide, throughout the entire duration of pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide
- She understands and agrees to inform the Investigator if a change or stop of method of contraception is needed
- She must 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 pomalidomide as soon as it is dispensed following a negative pregnancy test
- She understands and accepts the need to undergo pregnancy testing based on the frequency outlined in this plan (Section 2.4) and in the Informed Consent
- She acknowledges that she understands the hazards pomalidomide can cause to an unborn fetus and the necessary precautions associated with the use of pomalidomide.

The Investigator must ensure that a FCBP:

- Complies with the conditions of the pregnancy prevention plan, including confirmation that she has an adequate level of understanding
- Acknowledges the aforementioned requirements.

2.2.2 Females Not of Childbearing Potential

For a FNCBP, pomalidomide is contraindicated unless all of the following are met (ie, all FNCBP must be counseled concerning the following risks and requirements prior to the start of pomalidomide):

- She acknowledges she understands the hazards pomalidomide can cause to an unborn fetus and the necessary precautions associated with the use of pomalidomide.

2.2.3 Males

The effect of pomalidomide on sperm development is not known and has not been studied. The risk to an unborn baby in females of child bearing potential whose male partner is receiving pomalidomide is unknown at this time. Therefore, male subjects taking pomalidomide must meet the following conditions (ie, all males must be counseled 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 FCBP
- 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 FCBP l.
- Understand the potential teratogenic risk if the subject donates semen or sperm.

2.3 Contraception

2.3.1 Female Subjects of childbearing Potential

Females of childbearing potential enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact during the following time periods related to this study: 1) for at least 28 days before starting pomalidomide; 2) while taking pomalidomide; 3) during dose interruptions; and 4) for at least 28 days after the last dose of pomalidomide.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. If the below contraception methods are not appropriate for the FCBP, she must be referred to a qualified provider of contraception methods to determine the medically effective contraception method appropriate to the subject. The following are examples of highly effective and additional effective methods of contraception:

- Examples of highly effective methods:
  - → Intrauterine device (IUD)
  - → Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [e.g. desogestrel])
  - → Tubal ligation
  - → Partner's vasectomy
- Examples of additional effective methods:
  - → Male condom
  - → Diaphragm
  - → Cervical Cap

Because of the increased risk of venous thromboembolism in subjects with multiple myeloma taking pomalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a subject is currently using combined oral contraception the subject should switch to another one of the effective methods listed above. The risk of venous thromboembolism continues for 4 to 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 subjects with neutropenia.

2.3.2 Male Subjects

Male subjects must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide, even if he has undergone a successful vasectomy.

2.4 Pregnancy testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for FCBP.

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

Females of childbearing potential 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

taking pomalidomide, at study discontinuation, and at Day 28 following the last dose of pomalidomide.

Females of childbearing potential with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 14 days while taking pomalidomide, at study discontinuation, and at Days 14 and 28 following the last dose of pomalidomide.

2.5 Pregnancy Precautions for Pomalidomide Use

2.5.1 Before Starting Pomalidomide

2.5.1.1 Female Subjects of Childbearing Potential

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

Females of childbearing potential must use two reliable forms of contraception simultaneously, or practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact for at least 28 days before starting pomalidomide.

2.5.1.2 Male Subjects

Male subjects must agree to practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide, even if he has undergone a successful vasectomy.

2.5.2 During and After Study Participation

2.5.2.1 Female Subjects:

- Females of childbearing potential 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 taking pomalidomide, at study discontinuation, and at Day 28
- following the last dose of pomalidomide.
- Females of childbearing potential with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every

- 14 days while taking pomalidomide, at study discontinuation, and at Days 14 and 28 following the last dose of pomalidomide.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control if not committing to complete abstinence, or confirm commitment to complete abstinence.
- If a FCBP considers the need to change or to stop a method of contraception, the Investigator must be notified immediately.
- Counseling 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 subject, pomalidomide must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Pomalidomide must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding while taking pomalidomide and for at least 28 days after the last dose of pomalidomide.

2.5.2.2 Male Subjects:

- Must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or use a condom during sexual contact with a pregnant female or a FCBP while receiving pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide, even if he has undergone a successful vasectomy.
- Must not donate semen or sperm while receiving pomalidomide, during dose interruptions or for at least 28 days after the last dose of pomalidomide.
- Counseling 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 the partner of a male subject while taking pomalidomide, the Investigator must be notified immediately.

2.5.3 Additional precautions

- Subjects should be instructed to never give pomalidomide to another person.
- Subjects should be instructed to return any unused capsules to the study doctor.
- Subjects should not donate blood while receiving pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.
- No more than a 28-day pomalidomide supply may be dispensed with each cycle of pomalidomide.

Pomalidomide Education and Counseling Guidance Document

To be completed prior to each dispensing of pomalidomide.

Protocol Number: _____

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

- ☐ FCBP (Female of childbearing potential): a female who: 1) has achieved menarche (first menstrual cycle) at some point, 2) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 3) 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

2.6 Female of Childbearing Potential:

1. I have verified and counseled the subject regarding the following:
   - ☐ Potential risk of fetal exposure to pomalidomide: A teratogenic potential of pomalidomide in humans cannot be ruled out. 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. Females of childbearing potential must agree not to become pregnant while taking pomalidomide.
   - ☐ That the required pregnancy tests performed are negative.
   - ☐ The subject confirmed that she is using TWO reliable methods of birth control at the same time, or complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact (at least 28 days prior to receiving pomalidomide, while receiving pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide):

     One highly effective method and one additional method of birth control must be used AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:

     - Examples of highly effective methods:
       - ♦ Intrauterine device (IUD)
       - ♦ Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [e.g. desogestrel])
       - ♦ Tubal ligation

- ♦ Partner's vasectomy
- Examples of additional effective methods:
  - ♦ Male condom
  - ♦ Diaphragm
  - ♦ Cervical Cap

☐ The subject confirmed that even if she has amenorrhea she must comply with advice on contraception.

☐ Pregnancy tests before, during administration of pomalidomide and at the last dose of pomalidomide, even if the subject agrees not to have reproductive heterosexual contact.

☐ Frequency of pregnancy tests to be done:

- Two pregnancy tests will be performed prior to receiving pomalidomide, one within 10 to 14 days, and a second within 24 hours of the start of pomalidomide.
- Every week during the first 28 days of this study and a pregnancy test every 28 days while the subject is taking pomalidomide if menstrual cycles are regular.
- Every week during the first 28 days of this study and a pregnancy test every 14 days while the subject is taking pomalidomide if menstrual cycles are irregular.
- If the subject missed a period or has unusual menstrual bleeding.
- When the subject is discontinued from the study and at Day 28 after the last dose of pomalidomide 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 the last dose of pomalidomide.

☐ The subject confirmed that she will stop taking pomalidomide immediately in the event of becoming pregnant and to call her study doctor as soon as possible.

☐ The subject confirmed that she has not and will not breastfeed a baby while taking pomalidomide and for at least 28 days after the last dose of pomalidomide.

☐ The subject has not and will never share pomalidomide with anyone else.

☐ The subject has not and will not donate blood while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.

☐ The subject has not and will not break, chew, or open pomalidomide capsules at any point.

☐ The subject confirmed that she will return unused pomalidomide capsules to the study doctor.

2. I have provided the Pomalidomide Information Sheet to the subject.

2.7 Female not of childbearing potential (natural menopause for at least 24 consecutive months, a hysterectomy, or bilateral oophorectomy):

1. I counseled the female NOT of childbearing potential regarding the following:
   - ☐ Potential risk of fetal exposure to pomalidomide: A teratogenic potential of pomalidomide in humans cannot be ruled out. If pomalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby
   - ☐ The subject has not and will never share pomalidomide with anyone else.
   - ☐ The subject has not and will not donate blood while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.
   - ☐ The subject has not and will not break, chew, or open pomalidomide capsules at any point.
   - ☐ The subject confirmed that she will return unused pomalidomide capsules to the study doctor.
2. I have provided the Pomalidomide Information Sheet to the subject.

Do Not Dispense Pomalidomide if:

- **The subject is pregnant.**
- **No pregnancy tests were conducted for a FCBP.**
- **The subject states she did not use TWO reliable methods of birth control (unless practicing complete abstinence from heterosexual contact) at least 28 days prior to receiving pomalidomide, while receiving pomalidomide and during dose interruptions.**
- **The subject stated that she has or does not want to adhere to pregnancy precautions outlined within this PPP.**

Counselor Name (Print): _____

Counselor Signature: _____ Date:____/____/___(dd/mmm/yyyy)

Maintain a copy of the Education and Counseling Guidance Document in the subject's records.

3 POMALIDOMIDE EDUCATION AND COUNSELING GUIDANCE DOCUMENT FOR MALE SUBJECTS

To be completed prior to each dispensing of pomalidomide.

Protocol Number: _____

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

1. I have verified and counseled the subject regarding the following:
   - ☐ Potential risk of fetal exposure to pomalidomide: A teratogenic potential of pomalidomide in humans cannot be ruled out. If pomalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby.
   - ☐ The subject confirmed that he has practiced complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or used a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or FCBP, while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.
   - ☐ The subject confirmed that he has not impregnated his female partner while in the study.
   - ☐ The subject confirmed that he will notify his study doctor if his female partner becomes pregnant and the female partner of a male subject taking pomalidomide confirmed that she will call her healthcare provider immediately if she becomes pregnant.
   - ☐ The subject has not and will never share pomalidomide with anyone else.
   - ☐ The subject confirmed that he has not donated and will not donate semen or sperm while taking pomalidomide or during dose interruptions and that he will not donate semen or sperm for at least 28 days after the last dose of pomalidomide.
   - ☐ The subject has not and will not donate blood while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.
   - ☐ The subject has not and will not break, chew, or open pomalidomide capsules at any point.
   - ☐ The subject confirmed that he will return unused pomalidomide capsules to the study doctor.
2. I have provide the Pomalidomide Information Sheet to the subject.

Do Not Dispense Pomalidomide if:

- **The subject stated that he has or does not want to adhere to pregnancy precautions outlined within this PPP.**

Counselor Name (Print): _____

Counselor Signature: _____ Date:_____/_____/____(dd/mmm/yyyy)

Maintain a copy of the Education and Counseling Guidance Document in the subject's records.

4 POMALIDOMIDE INFORMATION SHEET

FOR SUBJECTS ENROLLED IN CLINICAL RESEARCH STUDIES

Please read this Pomalidomide Information Sheet before you start taking pomalidomide 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?

1. **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 rats and rabbits.

   If you are a female who is able to become pregnant:

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

If you are a female not able to become pregnant:

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 an unborn baby in females whose male partner is receiving pomalidomide is unknown at this time.

- Male subjects (including those who have had a vasectomy) must practice complete abstinence or must use a condom during sexual contact with a pregnant female or a female that can become pregnant:
  - While you are taking pomalidomide
  - During breaks (dose interruptions) of pomalidomide
  - For at least 28 days after the last dose of pomalidomide
- **Male subjects should not donate sperm or semen** while taking pomalidomide, during breaks (dose interruptions) and for at least 28 days after the last dose of pomalidomide.
- **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 become pregnant.**

2. All Subjects
   - **Do not share pomalidomide 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 pomalidomide, during breaks (dose interruptions) and for at least 28 days after the last dose of pomalidomide.
   - **Do not break, chew, or open pomalidomide capsules at any point.**
   - You will get no more than a 28-day supply of pomalidomide at one time.
   - Return unused pomalidomide capsules to your study doctor.

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

APPENDIX 7 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for the Revised Protocol 02, 22-May-2018

Revised Protocol 02 incorporates changes required by the FDA per the partial clinical hold that was based on safety concerns from pembrolizumab studies Keynote 183 and 185. Study design and objective changes to reflect endpoints adequacy in light of these safety concerns were also incorporated. Additional changes include the revision of efficacy assessments in the protocol to align with the current International Myeloma Working Group (IMWG) guidance [redacted]

Revisions pertain to both present and future subjects.

The revisions of Revised Protocol 02 should be implemented once IRB/IEC/HA approval is received.

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title page	Change in BMS study personnel.	Administrative change
Title page, Synopsis	Elotuzumab has been removed from the title of the study.	Title updated to reflect the removal of the exploratory NE-Pd arm.
Synopsis, Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s)	Exploratory Arm (NE-Pd: Arm C) is closed to enrollment.	To focus enrollment on the investigational and control arms, the exploratory NE-Pd arm was removed.
Synopsis Objectives Section 1.5 Objective(s)	• Changed objective response rate (ORR) from primary to secondary objective. • Promoted overall survival (OS) from exploratory objective to secondary objective.	Based on pembrolizumab data, BMS deemed ORR as a co-primary endpoint for an accelerated approval strategy is no longer adequate. Progression free survival (PFS) is a clinically relevant surrogate endpoint for efficacy. As the gold standard for efficacy, OS was upgraded to secondary objectives.
Synopsis, Study Design, Study Schema Section 3.1 Study Design and Duration Figure 3.1-1 Study Design Schematic	• Exploratory NE-Pd arm is removed from study design. • Cross-over was removed. • Sample size and randomization ratio were updated to reflect that only N-Pd and Pd arm are continuing enrollment. • Study schema was updated.	• To focus enrollment on the investigational and control arms, the exploratory NE-Pd arm was removed. • Cross-over was stopped as of 1 Sept 2017 per the FDA request.
Synopsis Study Population Section 3.3.1 Inclusion Criteria	Clarified definitions of 'refractory' and 'relapsed and refractory' definitions.	To align with IMWG definitions.

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis, Statistical Considerations Section 8 Statistical Considerations	• Updated Sample Size Determination to reflect the change in study design (ie, removal of NE-Pd arm). • Updated Populations for Analyses, Endpoints, Efficacy Analyses, and Interim Analyses for efficacy to reflect the changes in study objectives (ie, primary objective changed from co-primary (ORR and PFS) to PFS only). • Added an Interim analysis for futility (ie, 50% of total events within N-Pd and Pd arms)	Statistical considerations section was updated to reflect the changes in study design and study objectives.
Section 1.7 Overall Risk/Benefit Assessment	Add information on the safety risk concerns from the pembrolizumab studies and how they affected this study.	Language was added to inform study investigators of the safety risks concerns from the pembrolizumab studies communicated by the FDA, the partial clinical hold placed on the study by the FDA in light of these concerns, and the stopped cross-over from the control Pd arm to the exploratory NE-Pd arm that FDA required amongst the hold conditions.
Section 3.3.2 Exclusion Criteria Criterion 2 Medical History and Concurrent Diseases c)	Updated to active systemic infection	Systemic added for clarification
Section 3.3.2 Exclusion Criteria 3. Prior Therapy or Surgery	New exclusion criteria of plasmapheresis within 4 weeks of randomization.	Plasmapheresis may interfere with eligibility assessments for measurable disease and with quantification of baseline value for M protein/ sFLC necessary for accurate response assessment. This exclusion criterion was inadvertently omitted in earlier protocol version.
	New criterion added: subjects who have received a live / attenuated vaccine within 30 days of first treatment are excluded.	Updated exclusion for nivolumab protocols.
Section 3.4.1 Prohibited and/or Restricted Treatments	Any live / attenuated vaccine (eg varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella (MMR)) is prohibited during treatment and until 100 days post last dose.	Update for nivolumab protocols.
Section 4.5.1.1.1 Pomalidomide	Removed requirement for pomalidomide administration at least 2 hours prior to nivolumab dosing.	To align with pomalidomide package insert.

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 4.5.4.4, Nivolumab	Updated criteria for dose delays and discontinuation for nivolumab.	Alignment with nivolumab program standard.
Section 5.1 Flow Chart/Time and Events Schedule	• Clarified requirements for efficacy assessments. • Included new schedule of bone marrow aspirate collection for [redacted] disease assessments.	• Aligned more clearly with IMWG guidance [redacted]
Section 5.4 Primary Efficacy	• Clarified requirements for safety assessments • Included new schedule of bone marrow aspirate collection for [redacted] disease assessments	• Clearer alignment with IMWG guidance. [redacted]
[redacted]		
Section 12, References	New references added to support protocol revisions	
Appendix 3	IMWG efficacy assessments updated	Alignment with current IMWG standards.
Appendix 6	Pomalidomide Pregnancy Risk Prevention Plan	Added appendix.
Throughout	Minor editorial and formatting changes.	