

Official Title of Study:

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

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**STATISTICAL ANALYSIS PLAN**

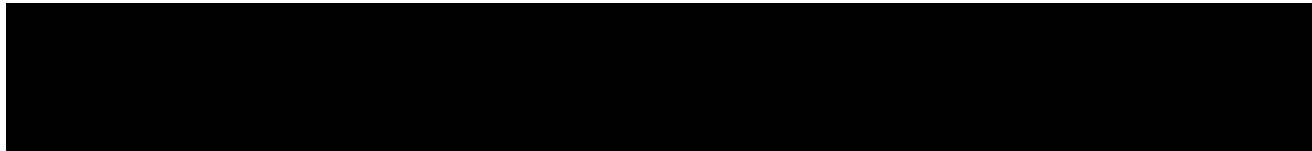
**A PHASE 2, MULTIPLE COHORT STUDY OF ELOTUZUMAB IN COMBINATION WITH POMALIDOMIDE AND LOW DOSE DEXAMETHASONE (EPD), AND IN COMBINATION WITH NIVOLUMAB (EN), IN PATIENTS WITH MULTIPLE MYELOMA RELAPSED OR REFRACTORY TO PRIOR TREATMENT WITH LENALIDOMIDE**

**PROTOCOL CA204-142**

**V 2.3**

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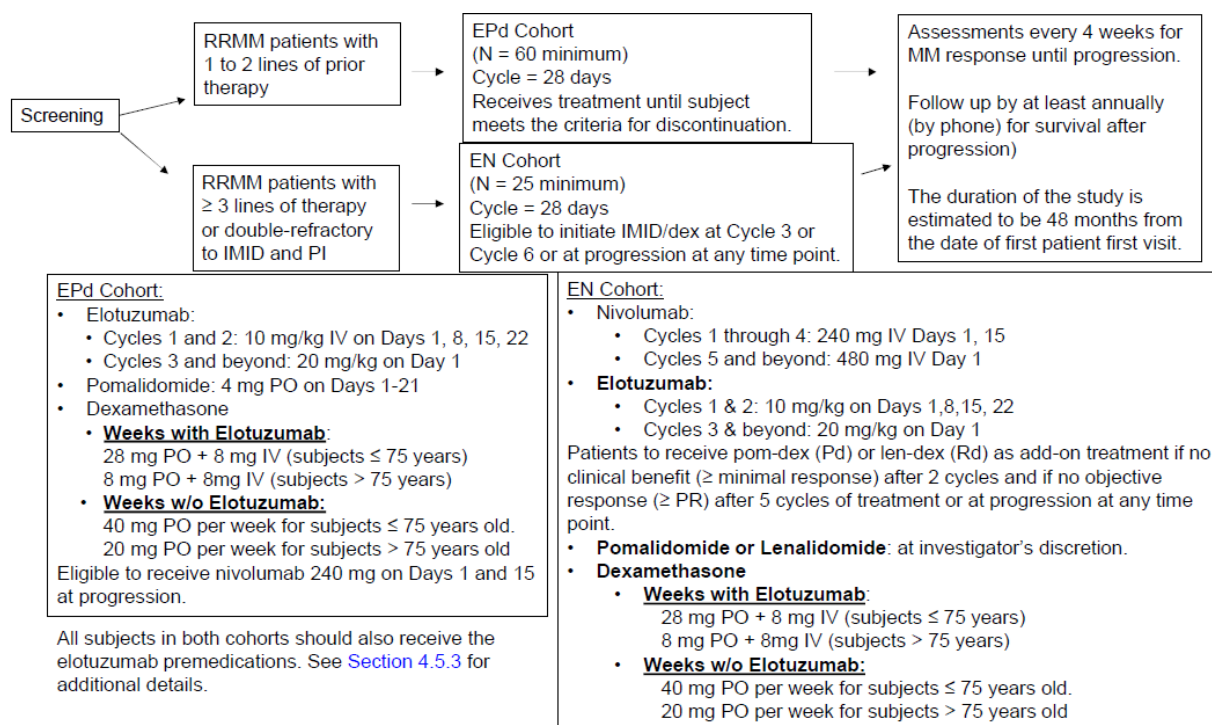
## 2 STUDY DESCRIPTION

### 2.1 Study Design

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

Approximately 100 subjects will be screened in this study. A minimum of 60 subjects will be treated in the EPd Cohort. Approximately 25 subjects will be treated in the EN Cohort. The estimated duration of enrollment is 18 to 24 months, and the duration of the study is estimated at 48 months from the date of first patient first visit.

The study design schematic is presented in Figure 3.



**Figure 3: Study design Schematic**

In the EPd Cohort, subjects will receive treatment with elotuzumab in combination with pomalidomide and low-dose dexamethasone in a 28 day cycle. Subjects will receive 10 mg IV

elotuzumab on Days 1, 8, 15, and 22 of Cycles 1 and 2. Starting with Cycle 3, subjects will receive 20 mg/kg on Day 1. As of Amendment 02, subjects who progress as defined by IMG criteria in the EPd cohort will be eligible to add nivolumab 240 mg every 2 weeks (Q2W) on Days 1 and 15 of each cycle.

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

## 2.2 Blinding and Unblinding

All subjects with eligibility of enrollment after the screening will be treated with IP/non-IP as indicated in Figure 3.

## 2.3 Blinding and Unblinding

Not applicable.

## 2.4 Protocol Amendments

Revised Protocol 01 (16-May-2016) incorporates Amendment 01, Administrative Letters 01 and 02:

Amendment 01 16-May-2016:

- Patients with multiple myeloma who may have received prior treatment with elotuzumab outside of a clinical trial are now eligible, provided the patient did not discontinue treatment due to intolerability to elotuzumab
- The requirement of 6 months or less for relapse to prior treatment with lenalidomide has been removed as a criteria for eligibility.
- Monthly dosing of elotuzumab will now begin at Cycle 3 rather than at Cycle 7.

Administrative Letter 02, 14-Dec-2015: Personnel changes

Administrative Letter 01, 21-Sep-2015: Alignment of the following protocol sections with revised washout period for study drug:

1. Protocol Sections 3.3.1 Age and Reproductive Status
2. Protocol Table 5.1-3 Pregnancy Test Note
3. Protocol Table 5.3.4-1 Pregnancy Test Note
4. Protocol Section 6.4 Pregnancy

Revised Protocol 02 (15-Feb-2017) incorporates Amendment 02. Amendment 02 15-Feb-2016:

- Allows subjects who received elotuzumab in combination with pomalidomide and low-dose dexamethasone (EPd Cohort) to receive nivolumab upon progression.

- Adds a cohort to receive elotuzumab in combination with nivolumab in a separate cohort (EN Cohort).

Revised Protocol 03 draft (08-Feb-2018)

- Exploratory objective for EPd cohort have been removed.
- Removed the option to add nivolumab to EPd cohort, removed the option to add pomalidomide/lenalidomide to the EN cohort, added the option for EN patients to crossover to EPd if they not respond to EN treatment.
- Increased the EN cohort size to 30 patients.

## **2.5 Independent Data Monitoring Committee and Other External Committees**

Not applicable.

## **3 OBJECTIVES**

### **3.1 Primary**

The primary objectives of this study is to estimate the PFS in patients with MM treated by EPd as second or third line regimen after relapse or being refractory or intolerant to a prior lenalidomide-based regimen, and to estimate the ORR in EN Cohort.

### **3.2 Secondary**

The secondary objectives are:

- To estimate the ORR and Overall Survival (OS) rate for EPd Cohort.
- To estimate the PFS and OS for EN Cohort.

[REDACTED]

[REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

## **4 ENDPOINTS**

### **4.1 Progression Free Survival (PFS)**

#### **4.1.1 *Definition of an Adequate Tumor Assessment***

In the analysis of PFS, subjects who do not progress are censored. A non-progressing subject can be censored on the date of a tumor assessment only if there is sufficient information to rule out progression. An “adequate” tumor assessment visit for ruling out progression will require the following information:

- Serum monoclonal paraprotein results, if measurable at baseline by central lab, and
- Urine monoclonal paraprotein results, if measurable at baseline
- Serum free light chain results, if measurable at baseline by central lab. This is only relevant for subjects who do not have measurable serum and urine monoclonal paraprotein results.

#### **4.1.2 *Date of Progression or Censoring When Different Components of a Tumor Assessment are Conducted at Different Times***

As different tumor measurements may be conducted on different days, for instance, the blood draw for serum M-protein may be on a different date than 24-hour urine, the investigators were instructed to report the earliest date of the measurements associated with that time point for progression. In contrast, if tumor measurements are done on different dates and the subject is being censored, instructions were to report the latest date of the measurements associated with that time point.

#### **4.1.3 *Primary Definition of Progression-Free Survival***

Progression Free Survival (PFS) is defined as the time from first dosing date to the date of the first documented progression per IMWG uniform criteria or death due to any cause, whichever occurs first. Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last adequate tumor assessment. Subjects who did not have any on study efficacy assessments and did not die will be censored on the first dosing date.

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

#### **4.1.4 *Secondary Definition of Progression-Free Survival***

Progression Free Survival (PFS) is defined as the time from first dosing date to the date of the first documented tumor progression per IMWG uniform criteria or death due to any cause, whichever occurs first. Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last adequate tumor assessment. Subjects who did not have any on study efficacy assessments and did not die will be censored on the first dosing date.

#### 4.2 Objective Response Rate (ORR)

The best overall response is determined as the best assessment based on all on-study efficacy data for the subject. Overall Response Rate (ORR) is defined as proportion of subjects with a best overall response of partial response (PR) or better.

#### 4.3 Overall Survival (OS)

Overall Survival (OS) is defined as the time from first dosing date to the date of death from any cause. A subject who has not died will be censored at last known date alive.

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[REDACTED]

[REDACTED]

#### 4.6 Safety and Tolerability

Safety and tolerability endpoints consist of all deaths, AEs, drug-related AEs, AEs leading to treatment discontinuation, SAEs, and drug-related SAEs and specific laboratory abnormalities (worst grade) collected during the treatment and up to 60 days after discontinuation of study drug will be tabulated using worst grade per NCI CTCAE v3.0 criteria by system organ class and MedDRA preferred term.

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## **5 SAMPLE SIZE AND POWER**

### **5.1 EPd Cohort**

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

Under the assumptions that:

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

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

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

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

### **5.2 EN Cohort**

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

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

## **6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES**

### **6.1 Study Periods**

There are three periods in this study: screening, on-treatment and post-treatment follow-up.

Screening: Most screening procedures must be done no more than 14 days prior to first dose of treatment. Some exceptions include Serum  $\beta$ 2-microglobulin, Pregnancy Test, Myeloma Urine and Serum Lab tests, Bone Marrow Aspiration/Biopsy, Skeletal Imaging, CT/MRI assessment for extramedullary soft tissue plasmacytoma, which can be done up to 60 days prior to first dose of study drug. See Section 5 of the Protocol for full details of study procedures and timings. For

analyses purposes data collected on or after information consent date and prior to first dose will fall into the screening/baseline period.

Baseline: Baseline evaluations will be those performed within 60 days prior to first dosing date. When an assessment is repeated multiple times within the screening period, the baseline evaluation will be the one closest to the first dosing date.

All laboratory tests and procedures done on the first date of dosing will be assumed to have occurred prior to dosing and therefore baseline evaluation for those parameters will be those prior or on the first dosing date.

On-Treatment Period: In the post baseline period, every 28 days is defined as a cycle. AEs will be defined as AEs with an onset date-time on or after the date-time of the first dose of study treatment (or with an onset date on or after the day of first dose of study treatment if time is not collected or is missing) and within 60 days of the last dose of study treatment. Subjects should have myeloma urine and serum laboratory assessments, and the tumor response assessments per IMWG uniform criteria will be every 4 weeks from date of first dose of study drug on Cycle 1 Day 1 until progression or discontinuation. Study treatment ends when the subject progresses, experiences unacceptable toxicity, or withdraws consent.

Follow-up Period: Subjects who are discontinued from further study treatment for reasons other than progression will be followed every 4 weeks for disease progression. Following disease progression, subjects will be followed at least annually for survival until the subject dies or the study ends.

## **6.2 Treatment Regimens**

The study is a Phase 2, multi-center, open-label, multiple cohort study of elotuzumab in combination with pomalidomide and low dose dexamethasone (EPd Cohort) and elotuzumab in combination with nivolumab (EN Cohort) in a 28 day cycle. The estimated duration of enrollment is 18 to 24 months, minimum of 24 months follow-up and study duration of about 48 months. This includes a up to 60 day screening period, a treatment period and a follow up period. The end of study will be defined as the date of the last visit of the last subject undergoing the study or death.

## **6.3 Populations for Analyses**

The following subject populations will be used for the statistical analysis:

All Enrolled Subjects: All subjects who gave signed informed consent;

ITT Subjects: All enrolled subjects who meet the inclusion and exclusion criteria;

All Treated subjects: This population includes all subjects who receive at least one elotuzumab dose. The safety analysis set is also the all treated analysis set.

# **7 STATISTICAL ANALYSES**

## **7.1 General Methods**

Continuous variables will be summarized using descriptive statistics; i.e. number of non-missing observations (n), mean, standard deviation (STD), median, minimum, maximum, first quartile

and third quartile. The number of decimal places displayed in all listings will be determined by the number of decimal places in the raw data. Unless otherwise specified, minimum and maximum will be reported to the precision as the data collected, one more decimal place for the mean and median, and two more decimal places for the standard deviation. The adjusted geometric mean, geometric mean ratio and the lower and upper limits of confidence interval will be displayed to three decimal places. Categorical variables will be summarized by frequencies and percentages.

Safety analyses will be conducted on all treated subjects. Efficacy analyses will be conducted on all treated subjects, and also by subgroups based on lines of prior therapy (2L, 3L), or by age group (<65 years, ≥65 years), and (<75 years, ≥75 years). Descriptive statistics (n, mean, median, standard deviation, minimum, maximum or interquartile range) will be provided. Because the sample size for the study is small, summary statistics with their associated 95% confidence intervals and tests of hypotheses will be based, to the extent possible, using small-sample statistics like the Clopper- Pearson for binomial data. Median time-to-event and its 95% confidence interval will be based on the Kaplan-Meier (KM) estimation procedure. The KM curves will be presented for time to event endpoints. Separate analyses will be conducted for each cohort EPd and EN.

Laboratory results, adverse events, and other symptoms will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 3.0, except where CTCAE grades are not available. Individual laboratory values will be presented in both the International System of Units (SI) and US unit (US). Adverse events will be categorized using the most current version of Medical Dictionary for Regulatory Activities (MedDRA), by system organ class and preferred term. Prior therapies will be summarized using the most current version of the World Health Organization (WHO) drug dictionary.

Statistical analyses will be carried out in SAS (Statistical Analysis System, SAS Institute, North Carolina, USA), unless otherwise indicated.

## **7.2 Study Conduct**

The study shall be conducted as described in approved protocol.

### **7.2.1 Accrual**

The following will be presented on all enrolled subjects:

- Number of subjects accrued by investigational site
- Number of subjects accrued by month

### **7.2.2 Relevant Protocol Deviations**

Eligibility and on-study deviations as required by guidelines will be summarized and listed for all treated subjects. A relevant protocol deviation is defined as a deviation from the protocol which is programmed in the database and which could potentially affect the interpretability of the study results.

- Subjects with relevant eligibility deviations:



- Subjects who have received 3 or more prior lines of therapy
- Subjects have no measureable disease at screening, based on central laboratory results, defined as one or more of the following
  - Serum IgG, IgA, IgM M-protein  $\geq 0.5$  g/dL
  - Urinary M-Protein  $\geq 200$  mg urinary M-protein excretion in a 24 hour collection sample
  - Involved serum free light chain (sFLC)  $\geq 10$  mg/dL provided the FLC ratio is abnormal.
- Subjects with on-study deviations:
  - Non-protocol specified systemic anti-myeloma therapy prior to discontinuation of study therapy
  - No baseline efficacy assessment. This occurs when there are no tumor assessments at all (laboratory assessments) on or prior to first day of dosing.

A by subject listing of relevant protocol deviations will be provided.

### **7.3 Study Population**

The intent-to-treat analysis set consists of enrolled subjects who meet the inclusion and exclusion criteria. The safety analysis set consists of subjects who receive treatment at least once. The safety analysis set is also the all treated subjects.

#### **7.3.1 Subject Disposition**

A frequency table of all enrolled subjects, broken out by whether or not they were treated, and giving reasons for not being treated, will be produced.

Subject disposition during the treatment period will be summarized. The number and percentage of subjects treated, still on treatment, discontinued from the treatment and reasons for discontinuation will be presented.

By-subject listings will also be produced to accompany the tables on enrollment and the subject disposition table.

In addition, a by-subject listing indicating whether the subject was included in each of the analysis populations will be provided.

#### **7.3.2 Demographic and Subject Characteristics**

Demographic and baseline characteristics will be summarized. The following parameters will be summarized; age at the time of informed consent (years), age category at time of informed consent (<65 years,  $\geq 65$  years), and (<75 years,  $\geq 75$  years), gender (Male, Female), race (White, Black/African American, American Indian/Alaska Native, Asian, Native Hawaiian/Other Pacific Islander, Other), ethnicity – for US subjects only (Hispanic/Latino, Not Hispanic/Latino), ECOG performance status (0, 1, 2, 3, 4, 5), time from disease diagnosis to first dose of study drug (months) and lines of prior therapy (2L vs. 3L).

An accompanying by-subject listing of demographic and subject characteristics will be presented for all treated subjects.

### **7.3.3 Disease Characteristics at Baseline**

Baseline disease characteristics will be summarized. The following parameters will be presented to summarize baseline disease:

- Myeloma Serum M-protein (g/dL)
- Myeloma Urine M-protein (mg/24 hours)
- Skeletal Imaging: number of lytic bone lesions
- CT/MRI assessment for extramedullary soft tissue plasmacytoma
- Bone Marrow Aspiration/Biopsy: percentage of plasma cells
- $\beta 2$  microglobulin (mg/L) (<3.5,  $\geq 3.5$ -5.5, >5.5)
- Albumin (g/L) (<3.5,  $\geq 3.5$ )
- ISS Stage at enrollment (I, II, III)
- Myeloma Type
- Disease Status (Relapsed and Refractory, Relapsed, Refractory, Intolerant). Intolerant subjects are classified in the CRF as “Neither Relapsed or Refractory”. All categories will be selected from CRF entries.

An accompanying by-subject listing of disease characteristics at baseline will be presented for all treated subjects. Laboratory results will be presented in standard international (SI) units and US units.

### **7.3.4 Prior Anti-Myeloma Therapy**

Prior systemic anti-myeloma therapy (which will be identified from the eCRF page “Prior Systemic Therapy for Multiple Myeloma”) will be categorized using the WHO drug dictionary and will be summarized. The latest version of the drug dictionary at the time of the analysis will be used.

A summary of the number and percentage of subjects receiving prior stem cell therapy and prior radiotherapy will be presented.

A by-subject listing containing relevant information on prior stem cell transplant, prior radiotherapy and prior systemic anti-myeloma therapy will be provided for all treated subjects.

### **7.3.5 General Medical History**

The number and percentage of subjects with any relevant medical history and by body system will be presented.

### **7.3.6 Physical Measurements**

Physical measurements will not be summarized.

A by subject listing of weight will be provided.

## 7.4 Extent of Exposure

### 7.4.1 Study Therapy

Pomalidomide, oral dexamethasone and IV dexamethasone are given at fixed doses and are not adjusted for body surface area or weight. The elotuzumab dose, in contrast, is adjusted for weight. Throughout this SAP, a subject’s elotuzumab dose level at a particular time point will refer to the actual dose, in mg/kg, rather than their planned dose. A subject’s actual elotuzumab dose level will be computed by dividing their total dose delivered, in mg, as recorded on the “Record of Study Medication - Elotuzumab” eCRF page, by their latest pre-dose weight, in kg, on Day 1 of that cycle.

#### 7.4.1.1 Duration of Study Therapy

The number of cycles of treatment received by subjects will be summarized (using n, mean, STD, median, min, max, q1 and q3).

*If there is no treatment interruption*, The duration of each treatment (elotuzumab, dexamethasone [oral and IV combined] and pomalidomide), in months, will be calculated as:

$$(date\ of\ last\ dose\ of\ the\ drug - date\ of\ first\ dose\ of\ the\ drug + 1) / 30.4375$$

*If there is treatment interruption*, The duration of each treatment (elotuzumab, dexamethasone [oral and IV combined] and pomalidomide), in months, will be calculated as:

$$(date\ of\ last\ dose\ of\ the\ drug - date\ of\ first\ dose\ of\ the\ drug - days\ of\ treatment\ interruption + 1) / 30.4375$$

Duration of each of the study treatments will be summarized.

**Table 2: Treatment Schedule**

Pomalidomide	Day 1 - Day 21				Day 1 - Day 21				Day 1 - Day 21			
Elotuzumab*	↓	↓	↓	↓	↓	↓	↓	↓	↓			
Dexamethasone	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓
Day	1	8	15	22	1	8	15	22	1	8	15	22
Cycle	Cycle 1				Cycle 2				Cycle 3 and beyond			
* Elotuzumab dose is 10mg/kg Cycle 1 and Cycle 2 then 20 mg/kg Cycle 3 and beyond												

#### **7.4.1.2 Dose Modifications**

##### **7.4.1.3 Elotuzumab**

##### **7.4.1.4 Dose Reduction**

Reduction of elotuzumab dosing is not permitted as per the protocol.

##### **7.4.1.5 Dose Delay**

Dose delays of elotuzumab beyond the allowed dosing window are not permitted as per the protocol. Delays within the allowed dosing window could be for logistical or no reasons and will not be summarized.

##### **7.4.1.6 Dose Omission**

An omission for elotuzumab will be calculated based on records from the dosing CRF page. If the interval between the two dosing dates for elotuzumab is > 10 days (in cycles 1, 2 or 3) or > 35 days (from cycle 3 onwards), the dose will be considered to have been omitted.

The number and percentage of subjects with a dose omission, and with 1, 2, 3, or  $\geq 4$  omissions will be summarized. For subjects with an omission, their reason for omission (from the dose modification page of the CRF) will be summarized in the groups: “hematologic toxicity”, “non-hematologic toxicity”, “AE”, “dosing error” and “other”. For subjects without an available reason for omission, the category “unknown” will be used.

A by-subject listing for dose omission will be presented for all treated subjects. This listing will include all reported omission per CRF, regardless of whether the subject had a computed omission based on the actual dosing dates.

##### **7.4.1.7 Infusion Interruption**

The number and percentage of subjects with any interruption in their elotuzumab infusion, with 1, 2, 3, or  $\geq 4$  interruptions, with an interruption due to “infusion reaction”, “infusion administration issues” and “other” will be presented. In addition, duration of interruptions (in minutes) will be summarized via descriptive statistics.

A subject listing will be generated for elotuzumab IV interruptions. This listing will include reason for interruption, whether the interruption was resumed, and duration of the interruption.

The number and percentage of subjects with any elotuzumab IV rate reduction, with 1, 2, 3, or  $\geq 4$  rate reductions, and with rate reductions due to “infusion reaction,” “infusion administration issues,” and “other” will be presented.

A listing will be generated for elotuzumab IV rate reductions.

##### **7.4.1.8 Pomalidomide**

The number and percentage of subjects with a dose reduction, omission and discontinuation which will be collected on the records from the dosing CRF page.

Reduction of Pomalidomide will also be computed based on the actual dose received. In any study day (excluding, cycle 1, day 1), the drug will have a calculated reduction compared to the

previous day, if the actual level of the administered dose is below the actual level of the administered dose in the previous instance. The information for this analysis will be derived programmatically, using the total daily dose on the “Record of Study Medication - pomalidomide” eCRF page. The daily dose levels are defined as follows:

- Dose level 0 or full dose (4mg)
- Dose level -1 (3mg)
- Dose level -2 (2mg)
- Dose level -3 (1mg)

The number and percentage of subjects with a dose reduction, and the lowest dose level achieved per subject (-1, -2, -3), will be presented.

The reason for dose reduction as reported by the investigator will be tabulated for all instances with a calculated reduction based on the dose modification for Pomalidomide page. A category “unknown” will be defined for all calculated reductions with no reason reported by the investigator.

The number of subjects with any reported dose changes including reduction, omission and discontinuation, with 1, 2, 3, or  $\geq 4$  reported dose changes will be provided. The reason for dose changes (from the dose modification page of the CRF) will be summarized in the groups: “hematologic toxicity”, “non-hematologic toxicity”, “AE”, “dosing error” and “other”. For subjects without an available reason for omission, the category “unknown” will be used.

A by-subject listing of dose reductions will be generated. This will include all reported reductions per investigator, regardless of whether it met the requirements for a calculated reduction

#### **7.4.1.9 Dexamethasone (Oral)**

For PO dexamethasone the following summaries will be produced:

- The number of subjects with any dose modification, and with a reason for the modification of “hematologic toxicity”, “non-hematologic toxicity”, “AE”, “dosing error” and “other”).
- The total number of modifications of the drug experienced by a subject, both overall and by the reason for the modification.

By subject listings of record of study medication for each of IV dexamethasone and PO dexamethasone will be provided.

#### **7.4.1.10 Cumulative Dose, Dose Intensity, and Relative Dose Intensity**

A subject’s cumulative dose of elotuzumab is measured in mg/kg, and is defined as the sum of their elotuzumab doses (mg/kg) (actual, not planned) over all infusions. Most recent weight will be used for the calculation. A subject’s cumulative dose of pomalidomide is defined as the sum of each dose they took, as recorded in their medication diary. In order to compute the cumulative dose of dexamethasone however, IV dexamethasone will have to be converted to its equivalent oral dose. This will be done by treating each mg of IV dexamethasone as 1.32mg of oral dexamethasone, i.e. making use of the fact that the mean bioavailability of oral dexamethasone

was estimated to be 0.76<sup>19</sup>). A subject's cumulative dose of dexamethasone will be defined as the sum of all dexamethasone doses, oral and IV, converted to oral equivalent. The cumulative dose administered will be summarized for each of these drugs.

**Elotuzumab:**

Elotuzumab dose intensity (mg/kg/week) per subject will be calculated separately for Cycles 1 and 2, and Cycle 3 and beyond, since elotuzumab dosing in Cycles 1 and 2, and Cycle 3 and beyond differ from each other.

Cycle 1 and 2:

7x[cumulative dose of Elotuzumab during the first 2 cycles/ (min(date of first dose of Elotuzumab in the last cycle among the first 2 cycles+28, discontinuation date, death date) - date of first dose of Elotuzumab in cycle 1)]

Cycle 3 and beyond:

7x[cumulative dose of Elotuzumab starting from Cycle 3 / (min(date of first dose of Elotuzumab in the last cycle+28, discontinuation date, death date) - date of first dose of Elotuzumab in cycle 3 )]

The relative dose intensity will be calculated as

$$(Dose\ Intensity/Planned\ Dose\ Intensity(PDI))\times 100\%$$

Planned dose per week for elotuzumab is 10mg/kg/week for the first 2 cycles, 5mg/kg/week for cycles 3 and beyond. The PDI per subject for elotuzumab will be computed by averaging the planned doses per week over the treatment duration e.g., planned elotuzumab PDI for a subject whose last dose was the first dose of third cycle would have the PDI computed as

$$Elotuzumab\ PDI\ ((mg/kg/wk) = \frac{4 \times 10 + 4 \times 10 + 4 \times 5}{12}$$

Dose intensity and relative dose intensity of elotuzumab will be summarized.

**Pomalidomide:**

Dose intensity and relative dose intensity for pomalidomide (mg/week) will be calculated as the standard daily dose, 4 mg from Day 1 to Day 21 during each cycle.

The pomalidomide dose intensity, per subject, will be calculated as:

7x[cumulative dose of pomalidomide / (min(date of first dose of Pomalidomide in the last cycle in which Pomalidomide was administered+28, discontinuation date, death date) - date of first dose of Pomalidomide )]

The relative dose intensity of pomalidomide is the dose intensity per week divided by the planned dose intensity per week, 21mg times 100%.

**Dexamethasone:**

The dose intensity (mg/week) of dexamethasone, per subject, will be calculated separately for the period encompassing Cycles 1 and 2 and for the periods from Cycles 3 and beyond.

Cycle 1 and 2:

$7x[\text{cumulative dose of Dexamethasone during the first 2 cycles} / (\text{min}(\text{date of first dose of Dexamethasone in the last cycle among the first 2 cycles} + 28, \text{ discontinuation date, death date}) - \text{date of first dose of Dexamethasone in cycle 1})]$

Cycle 3 and beyond:

$7x[\text{cumulative dose of Dexamethasone starting from Cycle 3} / (\text{min}(\text{date of first dose of Dexamethasone in the last cycle} + 28, \text{ discontinuation date, death date}) - \text{date of first dose of Dexamethasone in cycle 3})]$

**Table 3: 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 <sup>a,b</sup>	28 mg PO + 8 mg IV <sup>a,b</sup>	28 mg PO + 8 mg IV <sup>a,b</sup>	28 mg PO + 8 mg IV <sup>a,b</sup>
> 75 years old	Dexamethasone (mg)	8 mg PO + 8 mg IV <sup>a,b</sup>	8 mg PO + 8 mg IV <sup>a,b</sup>	8 mg PO + 8 mg IV <sup>a,b</sup>	8 mg PO + 8 mg IV <sup>a,b</sup>
Cycles 3 and beyond					
≤ 75 years old	Dexamethasone (mg)	28 mg PO + 8 mg IV <sup>a,b</sup>	40 mg PO per week <sup>c</sup>	40 mg PO per week <sup>c</sup>	40 mg PO per week <sup>c</sup>
> 75 years old	Dexamethasone (mg)	8 mg PO + 8 mg IV <sup>a,b</sup>	20 mg PO per week <sup>c</sup>	20 mg PO per week <sup>c</sup>	20 mg PO per week <sup>c</sup>

<sup>a</sup> On days of elotuzumab, infusion dexamethasone will be administered as a split dose of: 28 mg PO, for subjects ≤ 75 years old or 8 mg PO for subjects > 75 years old (between 3 - 24 hours before the start of elotuzumab infusion)

AND

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

<sup>b</sup> If elotuzumab dosing is skipped or discontinued, dexamethasone will be administered orally as in days without elotuzumab.

<sup>c</sup> Note the dexamethasone dose, as elotuzumab is not given on Days 8, 15 and 22 of cycle 3 and beyond.

The relative dose intensity of dexamethasone is the dose intensity per week divided by the planned dose intensity per week times 100%. The planned dose of dexamethasone (indicated in table 3) on elotuzumab dosing days, 8 mg IV dexamethasone plus 28 mg oral dexamethasone, is equivalent to 38.56 mg of oral dexamethasone for subjects ≤ 75 years old; similarly for subjects

> 75 years old, the planned dose on elotuzumab dosing days, 8 mg IV dexamethasone plus 8 mg oral dexamethasone, is equivalent to 18.56 mg of oral dexamethasone. The planned dose when dexamethasone is not being administered with elotuzumab is 40 mg per week for subjects  $\leq$  75 years old and 20 mg per week for subjects > 75 years old.

### **Nivolumab:**

The dose intensity (mg/week) of Nivolumab, per subject, will be calculated separately for the period encompassing Cycles 1 to 4 and for the periods from Cycles 5 and beyond.

Cycle 1-4:

$7 \times [\text{cumulative dose of Nivolumab during the first 4 cycles} / (\text{min}(\text{date of first dose of Nivolumab in the last cycle among the first 4 cycles} + 28, \text{ discontinuation date, death date}) - \text{date of first dose of Nivolumab in cycle 1})]$

Cycle 5 and beyond:

$7 \times [\text{cumulative dose of Nivolumab starting from Cycle 5} / (\text{min}(\text{date of first dose of Nivolumab in the last cycle} + 28, \text{ discontinuation date, death date}) - \text{date of first dose of Nivolumab in cycle 5})]$

The relative dose intensity of nivolumab is the dose intensity per week divided by the planned dose intensity per week, 120mg times 100%.

Descriptive statistics (n, mean, STD, median, min, max, q1 and q3) will be presented for the cumulative dose, and dose intensity of each agent. The number and percentage of subjects whose relative dose intensity falls into the following categories will be presented:  $\geq 90\%$ , 80% to < 90%, 70% to < 80%, 60% to < 70%, < 60%.

### **7.4.2 Premedication Other than Dexamethasone for Hypersensitivity Reactions**

A by-subject listing of pre-medication for elotuzumab, other than dexamethasone, will be provided for all treated subjects. This listing will be generated from the “Pre-medication for elotuzumab (other than Dexamethasone)” eCRF module and pre-medications will be coded using the BMS WHO drug dictionary.

### **7.4.3 Concomitant Medication**

Concomitant medications are medications, other than study medication or pre-medications for elotuzumab recorded on the “Pre-medication for elotuzumab” eCRF page, which are taken by subjects any time on-study, no earlier than the first day of study drug and no later than 60 days after the last dose of study drug. Concomitant medications will be coded using the BMS WHO drug dictionary. If there is clear evidence to suggest that the medication stopped prior to the first dose of study medication, the medication will be assumed to be Prior only.

The number and percentage of subjects taking any concomitant medication and each medication (Anatomical Therapeutic Chemical [ATC] classification system drug name) will be summarized, overall and by treatment group.

A by subject listing of concomitant medication will be provided.



#### **7.4.4 Discontinuation of Study Therapy**

The number and percentage of subjects who have discontinued study treatment and reason for discontinuation will be summarized using the subject status eCRF page from end of treatment. This is done in order to give a full accounting of all subjects who are off study treatment.

In addition, for subjects who discontinued one drug, while continuing at least one of the other two study drugs, their reason for treatment discontinuation will be summarized based on the dose modification CRF. Subjects will be counted in this summary if there is evidence from the dosing CRF that the subject received the combination therapy in at least one cycle, followed by additional cycles, where one of the drugs in the combination was discontinued.

### **7.5 Efficacy**

#### **7.5.1 Progression-Free Survival**

The primary analysis of this study is to estimate the two definitions of progression free survival (PFS) in all treated patients. The median PFS and 2-sided 95% confidence interval will be calculated via Kaplan-Meier (KM) estimation procedure. The PFS function will be estimated using the KM product limit method and will be displayed graphically. Estimates for 1-year, 2-year, and 3-year PFS rates will be presented along with their associated 95% CIs. These estimates will be come from the KM curve and their standard errors (SEs), for use in constructing CIs, will be computed using Greenwood's formula<sup>17</sup> and on log-log transformation applied on the survivor function.

Analyses of PFS will be conducted based on all treated population, and also by subgroups based on lines of prior therapy (2L/3L groups), or by age group (<65 years, ≥65 years), and (<75 years, ≥75 years). Subgroup analysis by ECOG PS (0-1,2), by response to most recent line of therapy (relapsed and refractory, relapsed, refractory, intolerant) and by ISS stage (I,II,III) if albumin and beta 2 microglobulin data are available will be conducted as well. PFS is also evaluated based on 3 levels of response (VGPR or better, PR, SD or MR). PFS will be estimated using the Kaplan-Meier (KM) product limit method and presented using a KM curve.

Time from last tumor assessment to data cut-off in months will be summarized by treatment arm and overall for all treated subjects. Subjects who have a PFS event will be considered as current for this analysis.

A by-subject listing will be presented including PFS duration on all treated population, whether the subject was censored, and if censored, the reason.

All of the analyses will be repeated for primary and secondary definitions of PFS.

#### **7.5.2 Overall Survival**

One of the secondary objective of this study is to estimate the overall survival (OS) in all treated subjects. The median OS and 2-sided 95% confidence interval will be calculated via Kaplan-Meier (KM) estimation procedure. The survival function will be estimated using the KM product limit method and will be displayed graphically. Estimates for 3-year, 4-year, and 5-year OS rates will be presented along with their associated 95% CIs. These estimates will be come from the

KM curve and their standard errors (SEs), for use in constructing CIs, will be computed using Greenwood's formula<sup>17</sup> and on log-log transformation applied on the survivor function.

Analyses of OS will also be conducted based on all treated population, and also by subgroups based on lines of prior therapy (2L/3L groups), or by age group (<65 years, ≥65 years), and (<75 years, ≥75 years). Subgroup analysis by ECOG PS (0-1,2), by response to most recent line of therapy (relapsed and refractory, relapsed, refractory, intolerant) and by ISS stage (I,II,III) if albumin and beta 2 microglobulin data are available will be conducted as well. OS is also evaluated based on 3 levels of response (VGPR or better, PR, SD or MR). OS will be estimated using the Kaplan-Meier (KM) product limit method and presented using a KM curve.

Currentness of OS data will be summarized in months, by computing the time from "last known alive" date to data cut-off date. Subjects who have a death event will be considered as current for this analysis.

A by-subject listing will be presented including OS duration, whether the subject was censored, and if censored, the reason, for all enrolled subjects.

### **7.5.3 Objective Response**

The other secondary objective of this study is to estimate the Objective Response Rate (ORR). The number and percentage of subjects in each category of best overall response (stringent CR [sCR], complete response [CR], very good partial response [VGPR], partial response [PR], minor (minimal response) [MR], stable disease/no change [SD], progressive disease [PD], or unable to determine [UD]) will be presented. An estimate of the objective response rate and an associated exact two-sided 95% CIs (Clopper and Pearson<sup>18</sup>) will be presented. Also, the number and percentage of subjects in each category of best overall response according to the investigator tumor assessment will be presented.

Analyses of ORR will be conducted based on the all treated analysis population, and also by subgroups based on lines of prior therapy (2L, 3L), or by age group (<65 years, ≥65 years), and (<75 years, ≥75 years). Subgroup analysis by ECOG PS (0-1,2), by response to most recent line of therapy (relapsed and refractory, relapsed, refractory, intolerant) and by ISS stage (I,II,III) if albumin and beta 2 microglobulin data are available will be conducted as well.

[REDACTED]

## 7.6 Safety

### 7.6.1 Adverse Events

AEs will be categorized using the most recent version of the MedDRA, by system organ class (SOC) and preferred term. The severity of AEs will be graded using the NCI CTCAE (v 3.0).

On-study AEs are defined as non-serious and serious AEs with an onset date on or after the first dose until 60 days after the last dose. See Section 8.4, Imputing AE Onset Dates, for a discussion of imputation rules for incomplete or missing AE onset dates. If the relationship to study drug is missing, then the AE will be assumed to be related to study drug.

Unless specified otherwise, AEs will be counted only once within each SOC and preferred term, according to their worst CTC grade.

Tables will be sorted by SOC and preferred term, with SOC ordered by decreasing frequency overall and then alphabetically. Preferred terms will be sorted within SOC by descending frequency overall and then alphabetically.

Frequency table of the worst grade of on-study AE will be presented. The table will be with AEs broken out by individual grade, 1, 2, 3, 4 or 5 together with an Any Grade category. There will also be a table in which grades are grouped as follows “Any, Grade 3-4 and Grade 5”. This last summary will be repeated for on-study drug-related AEs.

A by-subject listing all AEs will be presented for all treated subjects.

In addition the following will be presented:

- Exposure-adjusted AE incidence rates (including multiple occurrences of unique events) will be calculated for each SOC and preferred term.

Exposure-adjusted incidence rate per 100 person-years will be used and will be calculated as:

$$100 \times \frac{\text{Total number of unique AEs}}{\left( \frac{\text{subject date of last dose of study drug} - \text{subject date of first dose of study drug} + 60 + 1}{365.25} \right)}$$

and will be displayed along with a count of events

AEs can be counted multiple times within each SOC and preferred term in this summary table.

A by-subject listing of unique AEs will be provided for all treated subjects.

## **7.6.2 Serious Adverse Events and Adverse Event Leading to Discontinuation**

Summaries of worst grade of on-study SAE, both by individual grade (1, 2, 3, 4, or 5, together with an Any Grade category) and by grade grouped as “Any, Grade 3-4 and Grade 5” will also be presented. This last summary will be repeated for:

- On-study drug-related SAEs
- On-study AEs leading to discontinuation.
- On-study Drug related AEs leading to discontinuation

By-subject listings of SAEs and AEs leading to study drug discontinuation will be produced for all treated subjects.

## **7.6.3 Adverse Events of Special Interest**

### **7.6.3.1 Infusion Reactions**

Infusion reaction is a known elotuzumab toxicity. Two different approaches will be taken when defining infusion reaction.

The first way of defining infusion reaction will be based on investigator assessment. An investigator reported infusion reaction will be any non-serious or serious adverse event judged by the investigator to be infusion related start on the day or the day after the elotuzumab infusion.

A second approach will be to create a composite term called “peri-infusional adverse event”, which will be defined as any event from a pre-defined list of MedDRA terms (regardless of relationship to study drug) which starts on the day or the day after the elotuzumab infusion. See Appendix 2 for the list of preferred terms making up the composite term “peri-infusional adverse event”. The list of terms making up “peri-infusional adverse event” is broad and is expected to over-estimate the true incidence of clinically meaningful infusion reaction.

Frequency tables of the worst grade of on-study investigator infusion reaction will be presented, both by individual grade (1,2,3,4 or 5, together with an Any Grade category) and by grade grouped as “Any, Grade 3-4 and Grade 5”.

Worst grade for “peri-infusional adverse event” and “infusion reaction” will be presented, as Any, Grade 3-4 and Grade 5, only the preferred terms will be presented not the system organ class (SOC).

Listings for infusion reactions and peri-infusional adverse events will be provided.

### **7.6.3.2 Second Primary Malignancies**

A summary table and by-subject listing of second primary malignancies will be provided. Information on secondary malignancies will be obtained from the on-treatment eCRF page for secondary malignancies and the “Survival Status” eCRF page.

#### **7.6.4 Deaths**

The number and percentage of deaths and the investigator-reported cause of death will be presented. This will be summarized for all deaths, and for those reported on study treatment or within 60 days of discontinuing study treatment.

A by-subject listing will be provided and will present date of death and reason of death.

#### **7.6.5 Clinical Laboratory Evaluations**

On-treatment laboratory tests for safety are defined as those that occur after first dose of any study therapy until 60 days after last dose of any study therapy.

The number and percentage of subjects with each worst severity grade for on-study hematology parameters (hemoglobin, WBC, ANC, ALC and platelets) will be presented. Grades will be categorized as Grade 1, Grade 2, Grade 3, Grade 4, Any Grade and Grade 3-4. Subjects will be counted only once for each parameter, according to their worst post baseline CTC grade. The percentage of subjects with each worst severity grade will be calculated out of the number of all treated subjects with on-study assessment for lab parameter. Subjects without post-baseline (on-treatment) assessment for a lab parameter will be reported in the “NOT REPORTED” category.

This summary will be repeated for:

- Liver parameters (ALT, AST, alkaline phosphatase, albumin and total bilirubin) with available CTC grades
- Renal/electrolyte parameters (sodium, potassium, bicarbonate, calcium, glucose and creatinine) with available CTC grades

Sodium, potassium, calcium, and random glucose will be presented separately, based on their high and low values.

For blood urea nitrogen (BUN), direct bilirubin and total protein the worst category on-treatment will be presented. Results will be categorized as; below upper normal limits, above upper normal limits or not reported.

For reporting purposes, urea will be converted to BUN, using the conversion factor: urea (mmol/L) / 0.357 = BUN (mg/dL).”

Subjects experiencing any potential drug induced liver injury (DILI) will be summarized by treatment group and overall as follows:

- A summary of the number and percentage of subjects with (AST or ALT > 3 x upper limit of normal (ULN)) and (Total bilirubin > 2 x ULN and ALP < 2 x ULN) will be presented.

If any potential cases of DILI are identified then clinical review will be conducted to ensure no other immediate apparent possible causes of AT elevation and hyperbilirubinemia are present, including but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drugs known to be hepatotoxic.

Note: The timing for total bilirubin rising to > 2 x ULN needs to be concomitant with or within 30 days after ALT or AST rising to > 3 x ULN. ALP needs to be < 2 x ULN at the time of or

within 2 weeks before ALT or AST rising to > 3 x ULN or TBILI > 2 x ULN. This means a normal ALP value ( $\leq 2 \times \text{ULN}$ ) must be present within 2 weeks of either the ALT/AST criteria or the TBILI criteria.

A by subject listing of all laboratory data will be provided for all treated subjects. A separate listing will be provided for all subjects potentially experiencing DILI. A by subject listing of pregnancy test data will also be provided.

### **7.6.6 Vital Signs**

Vital Signs will not be summarized.

## **8 CONVENTIONS**

### **8.1 Age Definition**

Age (years) will be calculated as:

$$\frac{\text{date of informed consent} - \text{date of birth} + 1}{365.25}$$

### **8.2 Duration and Study Day Definition**

In instances in which study period between two dates are to be calculated (for example, duration of response, PFS and OS), the convention to be used is as follows: later date – earlier date + 1 day.

Study day is calculated as assessment date – first dose date + 1 day, if the assessment is taken on or after the first dose day. If the assessment is taken prior to the first dose day, study day will be calculated as assessment date – first dose date. Date of first dose is defined as Study Day 1.

### **8.3 Day Conversion of Date Imputation**

Conversion from days to months or years:

- 1 year = 365.25 days
- 1 month = 30.4375 days

Imputation for partial or missing progression dates:

- If only the day is missing, the 1<sup>st</sup> of the month will be used to replace the missing day.
- If the day and month are missing or a date is completely missing, the date of progression will be moved back to the last complete tumor assessment date.

In both the cases given above, the imputed date will still be considered an event.

Imputation for partial or missing death dates:

- If only the day is missing, the later of the last known alive date and the 1<sup>st</sup> of the month will be used to replace the missing day.
- If both the day and the month are missing, the later of the last known alive date and Jan 1<sup>st</sup> will be used to replace the missing information.

In both the cases given above, the imputed date will still be considered an event.

## **8.4 AE, Laboratory Results and Concomitant Medication**

Safety data will be handled according to the BMS safety data conventions (described in “Analysis of Safety Data - Reference to CT SOP 109”). This document includes descriptions on how to analyze AE data as well as how to handle partial dates, missing dates, and unknown end dates when analyzing safety data.

The following dictionaries will be used to code medical terms and to derive toxicity grades:

- Adverse events and other symptoms will be graded according to the NCI CTC Version 3.0 and categorized according to the latest version of MedDRA at the time of analysis.
- Laboratory results will be classified according to the CTC Version 3.0 grading system.
- All medications will be coded as per the latest version of the WHO Drug dictionary at the time of analysis.
- Tables and listings for laboratory results will be available in SI units and US units.

## **9 CONTENT OF REPORTS**

Statistical components for the clinical study report will be based on the content of this statistical analysis plan (SAP). It is assumed that a full CSR will be expected for the study CA204-142 at the writing of the SAP. If it is not the case, the SAP won't be updated. Details of the tables, listings, and figures to be prepared for the CSR will be included in a study-specific Data Presentation Plan (DPP).

### **9.1 Topline Analyses**

#### Study conduct:

- Relevant eligibility deviations (Table and Listing)

#### Subject population:

- End of Treatment Summary
- Demographic Characteristics Summary
- Response to Most Recent Line of Therapy Summary
- Time from Diagnosis to First Dose Date

#### Extent of exposure:

- Number of Cycles Summary

#### Tumor response:

- Best Overall Response

#### Progression free survival:

- Currentness of Follow-Up for PFS (Inv) Summary
- Kaplan-Meier plot of PFS Primary) (Figure)
- Kaplan-Meier plot of PFS (Secondary) (Figure)

Overall survival :

- Currentness of Follow-Up for Overall Survival Summary
- Kaplan-Meier plot of overall survival (Figure)

Safety:

- Adverse Event Summary by CTC Grade Combined
- Serious Adverse Event Summary by CTC Grade Combined
- Adverse Event Leading to Discontinuation Summary by CTC Grade Combined
- Infusion Reaction Summary by Common Terminology Criteria
- Deaths
- Deaths within 60 days of last study drug
- On study Hematology Lab Results
- On study Chemistry Lab Results

Specific tables corresponding to these topics will be identified in a separate Data Presentation Plan.

**10 DOCUMENT HISTORY**

<b>Table 4: Document History</b>		
<b>Version Number</b>	<b>Author(s)</b>	<b>Description</b>
0.1		Original version
0.2		Upated upon BMS comments on draft 1
0.3		Upated upon BMS comments on draft 2
0.4		Upated upon BMS comments
0.5		Updated upon protocol amendment 01
0.6		Updated upon protocol amendment 01 & BMS comments
1.0		Updated upon protocol amendment 01 & approved
1.1		██ ████████████████████
1.2		Updated upon protocol amendment 02 & BMS comments that include updates on draft amendment 03. There fore the SAP may not be consistent with the protocol whilst the amendment 03 is being finalized.
2.0		Updated upon draft of protocol amendment 03 received on 12Feb2018.
2.1		Added protocol amend 03 into section 2.4. Changed “last evaluable assessment” to “last adequate tumor assessment” ██ ████████████████████ Added sample size section 5.2 for EN cohort per amend 03





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**APPENDIX 1 LIST OF ABBREVIATIONS**

**Table 5: List of Abbreviations**

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BMS	Bristol Myers Squibb
CI(s)	Confidence Interval(s)
CR	Complete Response
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
ESRD	End Stage Renal Disease
HRQOL	Health Related Quality of Life
ITT	Intent-to-Treat
IV	Intravenous
IVRS	Interactive Voice Response System
Ld	Pomalidomide, (low-dose) Dexamethasone
E-Ld	Elotuzumab, Pomalidomide, (low-dose) Dexamethasone,
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple Myeloma
MR	Minor Response
ORR	Objective Response Rate
OS	Overall Survival
PD	Progression
PFS	Progression-Free Survival

**Table 5: List of Abbreviations**

PK	Pharmacokinetic
PO	Oral
PR	Partial Response
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sCR	Stringent Complete Response
SD	Stable Disease
SE	Standard Error
SI	International System of Units (SI)
SOC	System Organ Class
STD	Standard Deviation
UD	Unable to Determine
ULN	Upper Limit of Normal
VGPR	Very Good Partial Response
WHO	World Health Organization

**APPENDIX 2 LIST OF MEDDRA TERMS TO BE INCLUDED AS INFUSION REACTIONS (PERI-INFUSIONAL ADVERSE EVENTS)**

Infusion reaction is a known Elotuzumab toxicity and a composite term “peri-infusional adverse event” will be created. This composite term is defined as any of the following, and will be updated at the time of the analysis, using the latest version of MedDRA.

MedDRA terms with a start date on the day of or the day after an infusion:

**Table 6: MedDRA Terms**

- ACUTE RESPIRATORY FAILURE
- ALLERGIC COUGH
- ALLERGIC OEDEMA
- ALLERGIC RESPIRATORY SYMPTOM
- ANAPHYLACTIC REACTION
- ANAPHYLACTIC SHOCK
- ANAPHYLACTOID REACTION
- ANAPHYLACTOID SHOCK
- ANGIOEDEMA
- APNOEA
- BLOOD PRESSURE DECREASED

**Table 6: MedDRA Terms**

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BLOOD PRESSURE DIASTOLIC DECREASED  
BLOOD PRESSURE IMMEASURABLE  
BLOOD PRESSURE SYSTOLIC DECREASED  
BRADYCARDIA  
BRONCHIAL OEDEMA  
BRONCHOSPASM  
CARDIAC ARREST  
CARDIAC FAILURE ACUTE  
CARDIO-RESPIRATORY ARREST  
CARDIO-RESPIRATORY DISTRESS  
CARDIOVASCULAR INSUFFICIENCY  
CHEST DISCOMFORT  
CHILLS  
CHOKING SENSATION  
CIRCULATORY COLLAPSE  
CIRCUMORAL OEDEMA  
COUGH  
DIASTOLIC HYPOTENSION  
DIZZINESS  
DRUG HYPERSENSITIVITY  
DYSPHONIA  
DYSPNOEA  
ERYTHEMA  
EYE OEDEMA  
EYE SWELLING  
EYELID OEDEMA  
FACE OEDEMA  
FIRST USE SYNDROME  
FIXED ERUPTION  
FLUSHING  
GENERALISED ERYTHEMA  
HEADACHE  
HEART RATE INCREASED  
HOT FLUSH

**Table 6: MedDRA Terms**

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HYPERHIDROSIS  
HYPERPYREXIA  
HYPERSENSITIVITY  
HYPERVENTILATION  
HYPOTENSION  
HYPOXIA  
INFLUENZA LIKE ILLNESS  
INFUSION RELATED REACTION  
KOUNIS SYNDROME  
LARYNGEAL DYSPNOEA  
LARYNGEAL OEDEMA  
LARYNGOSPASM  
LARYNGOTRACHEAL OEDEMA  
LIP OEDEMA  
LIP SWELLING  
MYOCARDIAL INFARCTION  
NAUSEA  
OEDEMA  
OEDEMA MOUTH  
OROPHARYNGEAL SPASM  
OROPHARYNGEAL SWELLING  
OXYGEN SATURATION DECREASED  
PALPITATIONS  
PERIORBITAL OEDEMA  
PHARYNGEAL OEDEMA  
PRURITUS  
PRURITUS ALLERGIC  
PRURITUS GENERALISED  
PYREXIA  
RASH  
RASH ERYTHEMATOUS  
RASH GENERALISED  
RASH MACULAR  
RASH MACULO-PAPULAR

**Table 6: MedDRA Terms**

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RASH MACULOVESICULAR  
RASH PRURITIC  
RASH PUSTULAR  
RESPIRATORY ARREST  
RESPIRATORY DISTRESS  
RESPIRATORY FAILURE  
RESPIRATORY RATE INCREASED  
REVERSIBLE AIRWAYS OBSTRUCTION  
SENSATION OF FOREIGN BODY  
SHOCK  
SINUS TACHYCARDIA  
SKIN REACTION  
SKIN SWELLING  
SNEEZING  
STRIDOR  
SWELLING  
SWELLING FACE  
SWOLLEN TONGUE  
SYNCOPE  
TACHYCARDIA  
TACHYPNOEA  
THROAT IRRITATION  
THROAT TIGHTNESS  
TONGUE OEDEMA  
TRACHEAL OBSTRUCTION  
TRACHEAL OEDEMA  
TYPE I HYPERSENSITIVITY  
TYPE II HYPERSENSITIVITY  
TYPE IV HYPERSENSITIVITY REACTION  
UPPER AIRWAY OBSTRUCTION  
URTICARIA  
URTICARIA PAPULAR  
VASCULITIC RASH  
VASCULITIS

**Table 6: MedDRA Terms**

VOMITING  
WHEEZING

**APPENDIX 3 DEFINITIONS OF RESPONSE AND PROGRESSION CRITERIA (MODIFIED FROM IMWG)**

**Table 7: DEFINITIONS OF RESPONSE AND PROGRESSION CRITERIA (MODIFIED FROM IMWG)**

Response Subcategory	Response Criteria <sup>a</sup>
Stringent Complete Response (sCR)	CR, as defined below, plus the following: Normal FLC ratio <sup>b</sup> and absence of clonal cells <sup>c</sup> in bone marrow by immunohistochemistry or immunofluorescence.
Complete Response (CR) <sup>b</sup>	Negative immunofixation of serum and urine and disappearance of any soft tissue plasmacytomas, and < 5% plasma cells in bone marrow.
Very Good Partial Response (VGPR)	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or $\geq 90\%$ reduction in serum M-protein level plus urine M-protein level < 100 mg per 24 hour.
Partial Response (PR)	$\geq 50\%$ reduction of serum M-protein and reduction in 24-hour urinary M-protein by $\geq 90\%$ or to < 200 mg per 24 hour. If serum and urine M-protein are unmeasurable, a $\geq 50\%$ decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. In addition to the above criteria, if present at baseline, $\geq 50\%$ reduction in the size of soft tissue plasmacytomas is also required
Minor (Minimal) Response (MR)	25-49% reduction of serum M-protein and reduction in 24-hour urine M-protein by 50-89%, which still exceeds 200 mg per 24 hours. In addition, if present at baseline, 25-49% reduction in the size of soft tissue plasmacytomas is also required. No increase in the size or number of lytic bone lesions (development of compression fracture does not exclude response).
Stable Disease (SD)	Not meeting criteria for CR, VGPR, PR, MR, or progression.
Progressive disease	Any of the following: <ul style="list-style-type: none"> <li data-bbox="824 1749 1430 1806">• Increase of 25% from lowest response value in any one or more of the following: <ol style="list-style-type: none"> <li data-bbox="824 1818 1365 1854">1. Serum M-component (absolute increase must be</li> </ol> </li> </ul>

**Table 7: DEFINITIONS OF RESPONSE AND PROGRESSION CRITERIA (MODIFIED FROM IMWG)**

Response Subcategory	Response Criteria <sup>a</sup>
	<p><math>\geq 0.5</math> g/dL)<sup>d</sup> and/or</p> <p>2. Urine M-component (absolute increase must be <math>\geq 200</math> mg per 24 h) and/or</p> <p>3. Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be <math>&gt; 10</math> mg/dL)</p> <p>4. Bone marrow plasma cell percentage (absolute % must be <math>\geq 10\%</math>)</p> <ul style="list-style-type: none"> <li>• Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas</li> <li>• Development of hypercalcemia (corrected serum calcium <math>&gt; 11.5</math> mg/100 mL) that can be attributed solely to the plasma cell proliferative disorder</li> </ul>

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

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

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

<sup>d</sup> For progressive disease, serum M-component increase of  $\geq 1$  g/dL is sufficient to define progression if starting M-component is  $\geq 5$  g/dL