

STATISTICAL ANALYSIS PLAN

**AN OPEN LABEL, RANDOMIZED PHASE 2 TRIAL OF
POMALIDOMIDE/DEXAMTHASONE WITH OR WITHOUT ELOTUZUMAB IN
RELAPSED AND REFRACTORY MULTIPLE MYELOMA**

Protocol CA204-125

**FINAL
V 1.1**

Official Title of Study:

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LIST OF TABLES

[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

2.3 Blinding and Unblinding

Not applicable.

2.4 Protocol Amendments

Not applicable.

2.5 Independent Data Monitoring Committee and Other External Committees

Not applicable.

[REDACTED]

[REDACTED]

[REDACTED]

3 OBJECTIVES

3.1 Primary

The primary objective of this study is to compare progression free survival (PFS) between treatment arms.

3.2 Secondary

The secondary objectives are:

- To compare objective response rate between treatment arms
- To compare overall survival between treatment arms

[REDACTED]

4 ENDPOINTS

4.1 Endpoint Definitions

4.1.1 Progression-Free Survival

4.1.1.1 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 by central lab.

- 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.

4.1.1.2 Date of Progression or Censoring When Different Components of a Per Time Point Tumor Assessment 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.

4.1.1.3 Primary Definition of Progression-Free Survival (PFS)

PFS will be primarily analyzed applying an intent-to-treat (ITT) definition that utilizes all of the data on each randomly assigned subject at the time of the PFS analysis. PFS will be defined as the time from randomization to the date of the first documented tumor progression or death due to any cause. Clinical deterioration will not be considered progression. A subject who neither progresses nor dies will be censored on the date of their last adequate tumor assessment. A subject who does not have any post-baseline tumor assessments and who has not died will be censored on the date of randomization.

4.1.1.4 Secondary Definition of Progression-Free Survival

PFS will also be analyzed after censoring patients who either received subsequent therapy or had two or more missing tumor assessments prior to their disease progression or death. In this secondary definition, PFS will be measured as the time in months from randomization to the date of the first documented tumor progression or death due to any cause, provided death does not occur more than 10 weeks (2 or more assessment visits) after the last tumor assessment. Clinical deterioration will not be considered progression.

The following censoring rules will be applied for this definition of PFS:

- Subjects who receive subsequent anti-myeloma 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.
- Subjects who have an event (documented progression or death) > 10 weeks (2 assessment visits) after the last prior adequate tumor assessment will be censored at the last prior assessment.
- Subjects who neither receive subsequent therapy prior to progression nor have a progression event (including death) will be censored at their last adequate tumor assessment.
- In addition, subjects who do not have any post-baseline adequate tumor assessments and who do not die within 10 weeks of randomization will be censored on the date of randomization.

In all cases, if there are no adequate assessments for censoring then the patient is censored on the randomization date.

4.1.2 Objective Response Rate (ORR)

The best overall response is determined as the best assessment based on all on-study efficacy data for the subject.

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

4.1.3 Overall Survival

Overall survival is defined as the time from randomization to the date of death from any cause. If a subject has not died, their survival time will be censored at the date of last contact ("last known alive date"). Subject will be censored on the date of randomization if they were randomized but had no follow-up.

4.1.4 Time to Tumor Response

Time to response is defined as the time, in months, from randomization to the first objective documentation of PR or better. Time to response is restricted to the randomized subjects who achieved a best response of PR or better.

4.1.5 Duration of Response

Duration of response will be restricted to the randomized subjects with objective response of PR or better. It is measured from the time, in months, that the criteria for objective response are first met until the date of a progression event (according to the primary definition of PFS). A subject with objective response who does not have a progression event will be censored at the same time they were censored under the primary definition of PFS.

4.2 Pharmacokinetic Endpoints

The serum concentrations of elotuzumab at each time point (of the sampling schedule) will be summarized. The Cmin (minimum drug concentration observed) by study day will be summarized.

4.3 Immunogenicity Endpoints

Anti-drug antibody (ADA) is an immunogenicity endpoint. ADA will be evaluated using a validated bridging ligand binding method. For subjects who are found to have anti-elotuzumab antibodies, a titer will be reported to enable a qualitative comparison between subjects and within subjects at different time points.

4.4 Safety Endpoints

The safety endpoints include serious and non-serious adverse events, laboratory evaluations, deaths, and reasons off treatment.

[REDACTED]

5.1 Progression-Free Survival

The primary objective of the study is to compare the progression-free survival between the treatment arms in all randomized subjects. The number of events and power of this study were calculated assuming an exponential distribution for PFS in each arm.

The study will require at least 71 PFS events (progressions or deaths), for a two-sided experiment-wise $\alpha = 0.2$ log-rank test, to show a statistically significant difference in PFS between the treatment arms with 85% power when the true hazard ratio of the experimental arm to the control arm is 0.57. This is equivalent to demonstrating an improvement in median PFS from 4.0 months in the Pd arm⁹ to a median PFS of 6.8 months in the E-Pd arm.¹ A total of 105 subjects are to be randomized. Assuming approximately 10% of subjects may be lost to follow-up for the primary endpoint data, an additional 9 subjects would be randomized in the study. It is estimated that it would take approximately 9 months for full accrual of 114 subjects (assuming a fixed accrual rate of 13 subjects per month) and another 6 months to obtain the required number of events.

5.2 Objective Response Rate

Objective response rate is a secondary objective for this study. With a sample size of 114 subjects, there will be at least 90% power to detect a 23% improvement in response rate, using a two-sided 0.2 level test, in the E-Pd arm (to 58%) compared with a response rate of 35% in the Pd arm.

5.3 Overall Survival

OS is another secondary objective for this study. The final analysis of OS will be conducted after at least 78 deaths have been observed from 114 subjects. This is expected to happen 18 months (1.5 years) from the time of the final PFS analysis. With 78 events the study will have 75 % power using a two-sided log-rank test at a $\alpha = 0.2$ level, to show a statistically significant difference when the true hazard ratio is 0.64. This is equivalent to demonstrating a 56% improvement in median OS, i.e., 19.8 months in the E-Pd arm compared to the median OS in the Pd arm of 12.7 months.⁹

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 randomization. Some exceptions include efficacy assessments and ECGs, which can be done up to 28 days prior to randomization, and bone marrow which can be done up to 35 days prior to randomization. See Section 5 of the Protocol for full details of study procedures and timings. For analyses purposes

¹ Meletios A. Dimopoulos, Martha Q Lacy, et al. Pomalidomide in Combination with Low-Dose Dexamethasone: Demonstrates a Significant Progression Free Survival and Overall Survival Advantage, in Relapsed/Refractory MM: A Phase 3, Multicenter, Randomized, Open-Label Study Blood (ASH Annual Meeting Abstracts), Nov 2012; 120: LBA-6.

All enrolled subjects: All subjects who gave signed informed consent and who were entered in the IVRS.

Randomized subjects: All enrolled subjects who were randomized.

Treated subjects: This population includes all randomized subjects who received at least one dose of study medication (pomalidomide, dexamethasone or elotuzumab).

PK evaluable subjects: All treated subjects with at least one elotuzumab serum concentration data.

The analysis of baseline characteristics, efficacy and subject-reported outcomes will be carried out on the Randomized subjects population, with subjects grouped according to the treatment arm to which they were randomized. The analysis of extent of exposure and safety will be based on the Treated subjects population, with subjects grouped according to the treatment received, where treatment received is defined as the treatment arm to which they were randomized, unless they received the wrong treatment throughout the study.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

7.2 Study Conduct

7.2.1 Accrual Patterns

Tables summarizing accrual by center, country, region (North America, Europe, Japan, and Australia) overall and by treatment group will be generated (see [Appendix 3](#) for a list of countries in each region). Subject accrual will also be summarized by the randomization stratification factors per IVRS (number of lines of prior therapy (2-3 vs. ≥ 4) and ISS Staging at study entry (I-II vs. III)), overall and by treatment group. In addition, this summary will also be presented based on the stratification information obtained from the baseline CRF pages. A cross tabulation of IVRS vs. Baseline stratification factors will also be summarized.

7.2.2 Protocol Violations

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.

The number and percentage of subjects with any relevant protocol deviation and each specific deviation will be presented overall and by treatment group.

The following eligibility deviations are considered relevant in this study and will be summarized for all treated subjects:

- 1) Number of prior systemic anti-myeloma therapy is < 2
- 2) Non-measurable disease. This occurs when none of the following three conditions are met:
 - Serum IgG, IgA, or IgM M-protein $\geq 0.5\text{g/dL}$
 - M-protein $\geq 200\text{mg}$ in 24-hour urine
 - Involved serum free light chain (sFLC) $\geq 100\text{ mg/dL}$ provided the FLC ratio is abnormal
- 3) Ineligible for this study due to failure to meet criteria for refractory or relapsed and refractory MM. This occurs when:
 - Subjects did not progress (on or within 60 days of treatment) to their last treatment (not refractory).
 - Subjects did not fail treatment with a proteasome inhibitor and lenalidomide. This occurs when none of these take place:
 - i) “Refractory” to proteasome inhibitor and lenalidomide, and to their last treatment.
 - ii) “Relapsed and refractory” = patients had achieved at least a partial response to previous treatment with proteasome inhibitor or lenalidomide, or both, but progressed within 6 months, and were refractory to their last treatment.

Also, the following on-treatment deviations are considered relevant in this study and will be summarized for all treated subjects:

- 4) Non-protocol specified systemic anti-myeloma therapy prior to discontinuation of study therapy
- 5) Received non-assigned treatment regimen throughout the study
- 6) No baseline efficacy assessment. This occurs when there are no tumor assessments at all (laboratory assessments) on or prior to first day of dosing.
- 7) Subjects continuing to receive study therapy after 10 weeks of documented progression per investigator (as progression needs to be confirmed).

If assessments based on the central laboratory is unavailable, but the local laboratory results are available, then those will be used for evaluating deviations 2 and 6.

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

[REDACTED]

7.3.2 Demographic and Subject Characteristics

Demographic and baseline characteristics will be summarized, overall and by treatment group. The following parameters will be summarized; age at the time of informed consent (years), age category at time of informed consent (< 65 years, ≥ 65 years), and (< 75 years, ≥ 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), weight (kg), and ECOG performance status (0, 1, 2).

An accompanying by-subject listing of demographic and subject characteristics will be presented.

7.3.3 Disease Characteristics at Baseline

Baseline disease characteristics will be summarized, overall and by treatment group. The following parameters will be presented to summarize baseline disease:

- Serum M-protein (g/L)

- Urine M-protein (g/24 hours)
- Serum free light chain (g/L)
- Myeloma type (IgG, IgA, IgM, Light chain disease)
- Number of lytic bone lesions (0, 1-3, >3)
- Myeloma risk category
 - High risk: ISS stage II or III **and** t(4;14) or del(17p) abnormality
 - Low risk: ISS stage I or II **and** absence of t(4;14), del(17p) and 1q21 abnormalities and age < 55 years
 - Standard risk: any subjects not meeting the definition of high or low risk.
 - Not Evaluable: Subjects with missing data preventing their classification in the other 3 categories
- Individual FISH abnormalities (del 17p, t(14; 16), t(4; 14), del(1q), and del(1p))
- $\beta 2$ microglobulin (mg/L) (<3.5, ≥ 3.5 -5.5, ≥ 5.5)
- Albumin (g/L) (<3.5, ≥ 3.5)
- LDH (<300 IU/L, ≥ 300 IU/L)
- Soft tissue plasmacytomas (Yes, No)
- Refractory Status to prior lines of therapy:
 - Refractory to lenalidomide
 - Relapsed and refractory to lenalidomide
 - Refractory to proteasome inhibitor (PI)
 - Relapsed and refractory to proteasome inhibitor (PI)
 - Refractory to both PI and lenalidomide
 - Relapsed and refractory to both PI and lenalidomide
- ISS Stage (I, II, III) at enrollment and at diagnosis
- Time from disease diagnosis to randomization (months)

An accompanying by-subject listing of disease characteristics at baseline will be presented. All reports will be presented in standard international (SI) units and summaries in US units will also be available.

7.3.4 Prior Anti-Myeloma Therapy

Prior systemic anti-myeloma therapy (which will be identified from the eCRF page “Prior Therapy for Multiple Myeloma”) will be categorized using the WHO drug dictionary and will be summarized overall and by treatment group. The latest version of the drug dictionary at the time of the analysis will be used. The number and percentage of subjects with any prior systemic anti-myeloma therapy, the number and percentage of subjects who have received exactly 2, 3, and

≥4 prior lines of therapy, and the number of subjects receiving each therapy (generic term) will be presented.

A summary of the number and percentage of subjects receiving prior stem cell transplantation and prior radiotherapy will be presented overall and by treatment group.

A summary of the number and percentage of subjects receiving prior surgery related to cancer and each type of surgery (Kyphoplasty, Orthopedic surgery, Debulking surgery or Other) will be presented overall and by treatment group.

A by-subject listing containing relevant information on prior radiotherapy, prior surgery and prior systemic anti-myeloma therapy will be provided.

7.3.5 General Medical History

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

By subject listings of medical history will be provided. A by subject listing of pregnancy test data will also be provided.

7.3.6 Baseline Safety Laboratory Tests

Baseline safety laboratory evaluations will be the last available samples taken on or before Cycle 1, Day 1 and within 60 days of randomization.

Baseline safety laboratory values (both SI and US units) will be presented by CTC severity grade, by treatment group. Separate tables will be generated for hematology (hemoglobin, WBC, ANC [neutrophils plus bands], ALC [absolute lymphocyte count] and platelets [neutrophils plus bands]), liver function (ALT, AST, alkaline phosphatase, albumin and total bilirubin) and renal function/electrolytes (sodium, potassium, bicarbonate, calcium, glucose, and creatinine, creatinine clearance < 60ml/min, ≥ 60ml/min). Sodium, potassium, calcium, and random glucose will be presented separately, based on their high and low values.

CTC grades will be derived as part of the analysis data set programming using version 3.0.

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) by treatment group. A summary of the number of subjects taking each drug in each cycle will also be presented by treatment group.

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

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

Duration of each of the study treatments will be summarized by treatment group.

7.4.2 Dose Modifications

7.4.2.1 Elotuzumab Dose Reduction

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

7.4.2.2 Elotuzumab Dose Delay

A delay for elotuzumab will be computed based on records from the dosing CRF page. A delay in elotuzumab dosing will be defined as the number of days from the start date of the previous infusion to the start date of the current infusion being > 8 days and ≤10 days (if in cycles 1, 2 or cycle 3) or > 29 days and ≤ 35 days (from cycle 3 - onwards).

For courses with a delay of elotuzumab infusion, the time of delay in infusion will be summarized in the categories: 2-3 days, 4-7 days.

The number and percentage of subjects with any dose delay, with 1, 2, 3, or ≥ 4 reported delays will be summarized. For subjects with a delay, their reason for delay (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 delay, the category “unknown” will be used.

7.4.2.3 Elotuzumab 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 cycle 3) or > 35 days (from cycle 3 onwards), the dose will be considered to have been omitted.

For courses with an omission of elotuzumab infusion, the time between the previous and current infusion will be summarized in the categories: < 11 - 14, 15 - 21, 22-35, > 35 days.

The number and percentage of subjects with a dose omission, and with 1, 2, 3, or ≥ 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 delay and omission will be presented for all treated subjects. This listing will include all reported delays or omission per CRF, regardless of whether the subject had a computed delay or omission based on the actual dosing dates.

7.4.2.4 Elotuzumab Dose Interruption

The number and percentage of subjects with any interruption in their elotuzumab infusion, with 1, 2, 3, or ≥ 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.

7.4.2.5 Elotuzumab IV Rate Reduction

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

A by-subject listing will be generated for elotuzumab IV rate reductions

7.4.2.6 Pomalidomide Dose Reduction

Reduction of Pomalidomide will 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 by treatment group.

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.

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.

7.4.2.7 Pomalidomide Dose Interruption

In any cycle, the Pomalidomide dose will be considered as interrupted if there is a gap of two or more days between two dosing dates within that cycle where the patient did not receive the study drug. This will be calculated based on the information from the dose modification CRF for Pomalidomide.

The number and percentage of subjects with dose interruption, with 1, 2, 3, or ≥ 4 reported interruptions will be presented. For subjects with a computed interruption, their reason for interruption will be summarized from the dose modification CRF. For subjects without an available reason for interruption, the category “unknown” will be used.

7.4.2.8 Dexamethasone (IV) and Oral

Doses of Dexamethasone IV and oral will be categorized according to the following 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	

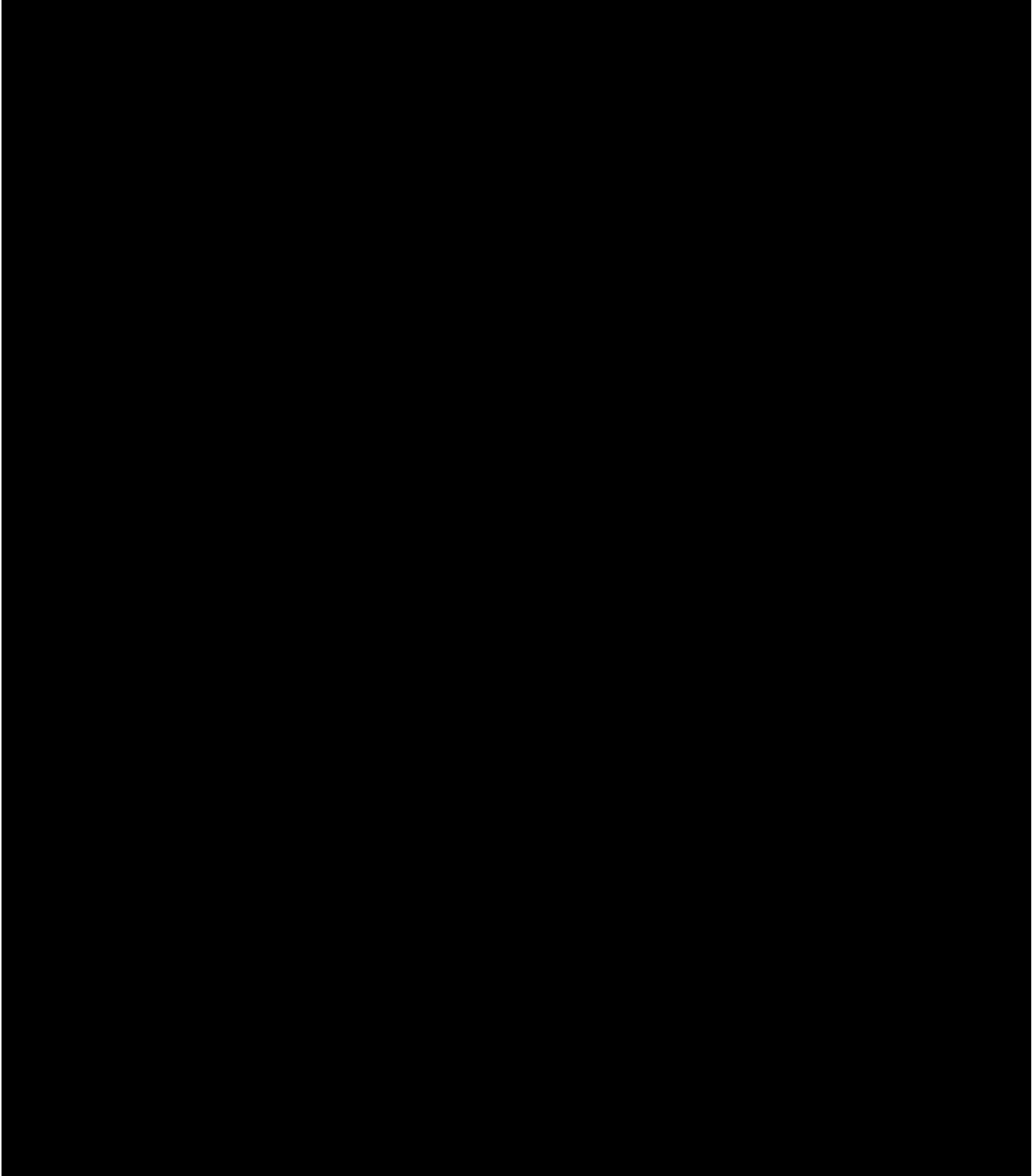
For IV dexamethasone the following summaries will be provided:

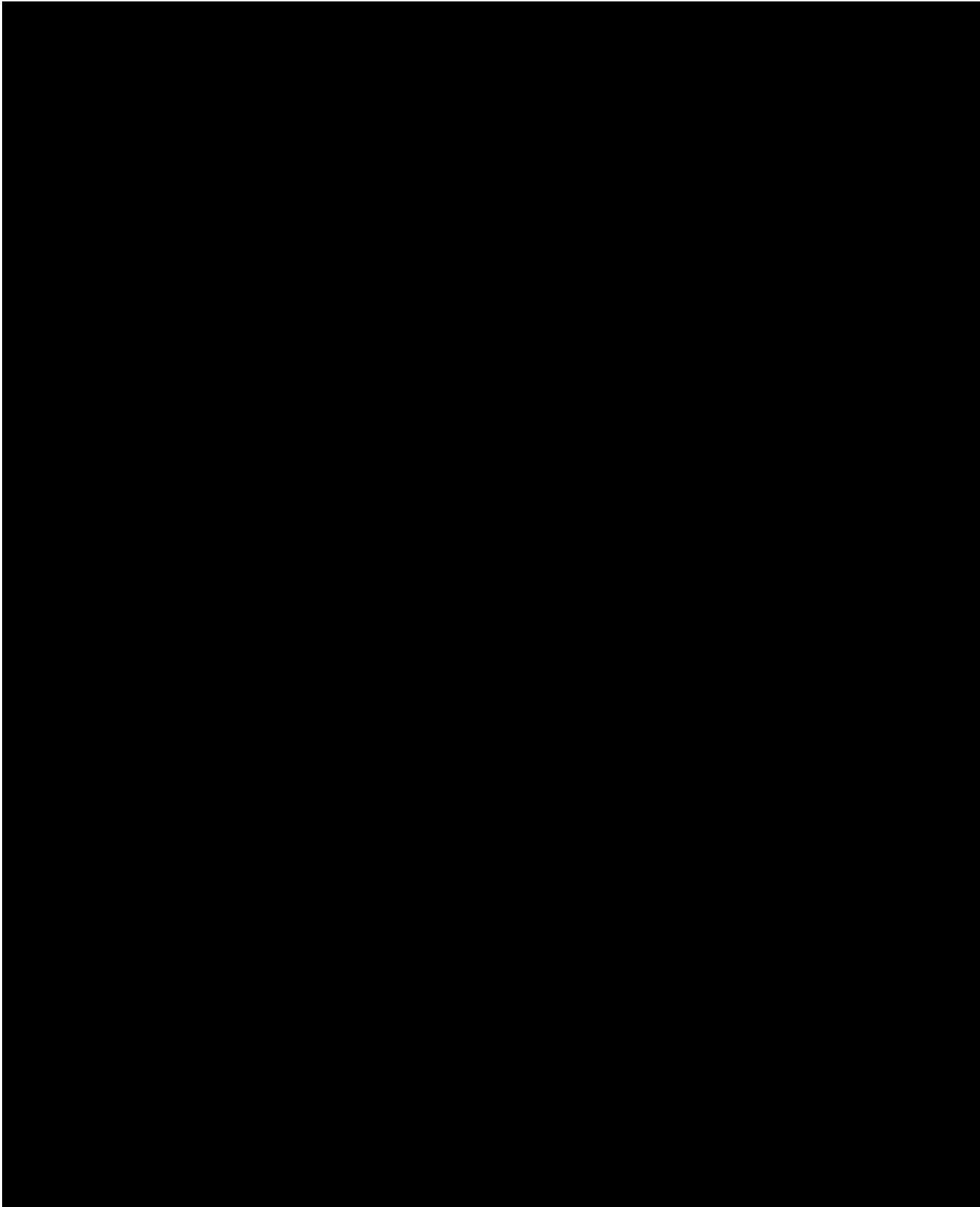
- The number of subjects with any dose delay, with 1, 2, 3, or ≥ 4 reported delays, and with a reason for delay of “hematologic toxicity”, “non-hematologic toxicity”, “AE”, “dosing error” and “other”.
- The number of subjects with any reported dose omission, with 1, 2, 3, or ≥ 4 reported omissions, and with a reported reason for omission of “hematologic toxicity”, “non-hematologic toxicity”, “AE”, “dosing error” and “other”.
- The number of subjects with any reduction in the dose of the drug, and with a reason for the reduction of “hematologic toxicity”, “non-hematologic toxicity”, “AE”, “dosing error”, and “other”).

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.





7.4.3 Premedication Other than Dexamethasone for Hypersensitivity Reactions

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

7.4.4 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.

7.4.5 Discontinuation of Study Therapy

The number and percentage of subjects who have discontinued all study treatment and reason for discontinuation will be summarized by treatment group and overall using the subject status eCRF page from end of treatment. This summary, unlike other analyses of exposure, will include all randomized subjects and will be grouped by treatment group as randomized. This is done in order to give a full accounting of all subjects who are off study treatment, including those who were randomized but never treated.

In addition, for subjects in the Elotuzumab arm, 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.

7.4.6 Subsequent Anti-Myeloma Therapy

The number and percentage of subjects with any subsequent systemic anti-myeloma therapy, reason for first subsequent systemic anti-myeloma therapy regimen (Documented progression of disease, Clinical deterioration without documented progression, Maintenance therapy without disease progression or clinical deterioration, or Other) and all subsequent systemic anti-myeloma therapy agents given categorized using the BMS WHO drug dictionary will be presented by treatment group.

The number and percentage of subjects with any subsequent surgery, type of first subsequent surgery (Kyphoplasty, Orthopedic surgery, Debulking surgery or Other) will be presented by treatment group.

The number and percentage of subjects with any subsequent radiation therapy will be presented by treatment group.

A by-subject listing of all subsequent surgery, all subsequent radiation therapy, and all subsequent systemic anti-myeloma therapy will be provided.

7.5 Efficacy

Efficacy analyses (PFS, ORR and OS) will be conducted on the population of all randomized subjects, grouped by arm assigned at randomization, unless otherwise noted.

Unless stated otherwise, whenever a stratified analysis is specified, the stratifications factors will be those used in the randomization (per IVRS), that is:

- Number of prior lines of therapy (2-3 vs. ≥ 4)
- ISS Staging at study entry (I-II vs. III)

The final analysis of PFS will occur after at least 71 progression events have been observed. This analyses will serve as the basis for the clinical study report. The final analysis of OS will be conducted after at least 78 deaths have been observed.

All p-values reported will be 2-sided. The alpha (α) level used for the two-sided CI will be same as nominal significance level for hypothesis testing ($\alpha = 0.2$). In addition two-sided 95% CI for these endpoints will also be provided. The p-values presented in the clinical study report will be rounded to the fourth decimal place. Point estimates and confidence bounds for efficacy variables will be rounded to the second decimal place.

7.5.1 Primary Analysis of Progression-Free Survival

The primary objective of this study is to compare PFS (based on the primary definition) across the two randomized arms. A two-sided $\alpha = 0.2$ log-rank test, stratified by number of lines of prior therapy (2-3 vs. ≥ 4) and ISS Staging at study entry (I-II vs. III) will be used to compare the PFS of subjects randomized to E-Pd to that of subjects randomized to Pd.

A stratified Cox proportional hazard model for PFS with treatment arm as single covariate will be used to report the hazard ratio of E-Pd to Pd and its corresponding 80% (and 95%) CI. The stratification factors will be the same as those used in the randomization.

The PFS function for each treatment arm will be estimated using the KM product limit method and will be displayed graphically. Median PFS will be estimated via the KM curve. Two-sided 95% CI for the median PFS will be computed for each randomized arm by the Brookmeyer and Crowley method using the log-log transformation of the survivor function.

The method of Gail and Simon¹² will be used to test for a qualitative interaction between treatment and strata, number of lines of prior therapy (2-3 vs. ≥ 4) and ISS Staging at study entry (I-II vs. III). This test will be conducted at the $\alpha = 0.10$ level and using the HR as estimate for treatment effect.

The proportional hazards assumption will be assessed via the following hazard rate model, which contains a time dependent covariate:

$$\lambda(t, z) = \lambda_i(t) e^{\{(b_1 + b_2 \times [\log(t)]) \times Z\}}, \quad i = \{1 - 4\}$$

where $i = 1 - 4$ corresponds to each of the four levels the stratum can take, and Z is the treatment indicator, which is equal to 1 for the combination arm and 0 for the control arm. The transformation of time is $\log(t)$. The null hypothesis, that the proportional hazards assumption is valid, i.e., that $b_2 = 0$, will be tested against the alternative hypothesis that $b_2 \neq 0$ using a Wald statistic.

Sensitivity analyses of PFS will also be conducted based on the secondary definition of PFS. These analyses will be the same as those specified above in [Section 7.5](#), Primary Analysis of PFS.

7.5.1.1 Supportive Analyses of Progression-Free Survival

The following supportive analyses will be conducted using both the ITT and the secondary definitions of PFS. P-values provided for these analyses are descriptive and will be used to evaluate the results in context of the primary analyses.

- 1) A multivariate Cox regression model will be used in order to estimate the treatment effect after adjustment for possible imbalances in known or potential prognostic factors. The factors used in the randomization, which, by definition, will be balanced across arms, will still be included in the model as stratification factors. However, all additional factors will be incorporated as covariates. The additional factors, which are all measured at baseline, will include: age (< 75 vs. ≥ 75), gender (male vs. female), ECOG PS (0-1 vs. 2), prior stem cell transplantation (yes vs. no), high myeloma risk (yes vs. no) [see [Section 7.5.1.2](#) for details], time from initial diagnosis, creatinine clearance (<60ml/min vs. ≥ 60 ml/min), and LDH (< 300IU/L, ≥ 300 IU/L).

The level of the covariate normally associated with the worst prognosis will be coded as the reference level:

- Age: ≥ 75
- Gender: Female
- ECOG: 2
- Prior stem cell transplantation: Yes
- High myeloma risk: Yes
- Time from initial diagnosis (\geq median)
- Creatinine clearance: < 60 ml/min
- LDH (≥ 300 IU/L)

The p-value associated with treatment and with each of the baseline covariates will be presented. The hazard ratio along with the associated 95% CI will also be presented. In addition, an 80% CI will be provided for the treatment effect.

- 2) PFS using stratification factors as obtained from the baseline CRF pages (instead of IVRS). The p-value and the hazard ratio associated with treatment will be presented along with the associated 2-sided 80% and 95% CIs. This analysis will be performed only if there is a difference of 10% in strata between the IVRS and CRF pages.
- 3) PFS using an un-stratified log rank test. The p-value and hazard ratio associated with treatment will be presented along with its associated two-sided 80% and 95% CIs.
- 4) PFS using an unstratified Cox proportional hazards model, adjusted, using as covariates only the two stratification factors used in randomization. The p-value and hazard ratio associated with treatment will be presented along with its associated two-sided 80% and 95% CIs.
- 5) PFS for subjects with no relevant deviation. These analyses will be conducted only if there are more than 5% subjects with relevant protocol deviations. The p-value and hazard ratio associated with treatment will be presented along with its associated two-sided 80% and 95% CIs.

A by-subject listing will be presented including treatment arm, PFS duration under the primary definition, PFS duration under the secondary definition, whether the subject was censored under the primary definition, and if censored, the reason, and whether the subject was censored under the secondary definition, and if censored, the reason.

7.5.1.2 Subset Analyses of Progression-Free Survival

The influence of baseline and demographic characteristics on the treatment effect will be explored via exploratory subset analyses for the following factors:

- Age (< 75 years, ≥ 75 years)
- Age (< 65 years, ≥ 65 years)
- Race (White, Black, Asian, Other)
- Gender (Male, Female)
- Baseline $\beta 2$ microglobulin (mg/L) (< 3.5 , ≥ 3.5)

- ISS Stage at study entry (I-II, III)
- Baseline LDH (< 300IU/L, ≥ 300IU/L)
- Baseline creatinine clearance (ml/min) (< 60, ≥ 60)
- Number of lines of prior therapy (2-3, ≥4)
- Region (North America, Europe, Japan, And Australia)
- Baseline ECOG performance status (0-1, 2)
- Prior stem cell transplant (Yes, No)
- Myeloma risk category (High risk, Low risk and Other)
 - High risk: ISS stage II or III **and** t(4;14) or del(17p) abnormality
 - Low risk: ISS stage I or II **and** absence of t(4;14), del(17p) and 1q21 abnormalities **and** age < 55 years
 - Standard risk: any subjects not meeting the definition of high or low risk and enough data to be classified as standard risk
- Individual FISH abnormalities (del 17p, t(14; 16), t(4; 14), del(1q), and del(1p))

The hazard ratio of E-Pd to Pd and the associated 95% CI for each subgroup category will be presented in a forest plot. The estimate of each hazard ratio and CI will be generated using an unstratified Cox proportional hazards model with treatment as the only covariate.

7.5.2 Analysis of Objective Response

The number and percentage of subjects in each category of best overall response per investigator assessment (stringent complete response [sCR], complete response [CR], very good partial response [VGPR], partial response [PR], minor response [MR], stable disease [SD], progressive disease [PD], or unable to determine [UD]) will be presented by treatment group. An estimate of the response rate and an associated exact two-sided 95% CI (Clopper and Pearson¹³) will be computed, by treatment group.

One of the secondary objectives is to compare the ORR in the two treatment groups using a two-sided $\alpha = 0.2$ level Cochran-Mantel-Haenszel (CMH) test stratified by the same factors used in the analysis of PFS. An estimate of the treatment odds ratio and corresponding two-sided 80% CI will be computed. A two-sided 95% CI will also be computed.

A 2-sided, 80% CI (along with 95% CI) for the difference of ORR between treatment arms will be computed for all randomized subjects by the method of DerSimonian and Laird¹⁴, using a fixed-effects model (setting Δ^2 equal to zero), adjusting for the stratification factors. The weighted response rate difference and 80% CI (along with 95% CI) can be determined using the following formula:

$$\hat{\theta} = \frac{\sum_{i=1}^4 \hat{\theta}_i w_i}{\sum_{i=1}^4 w_i} \sim N(\theta, 1 / \sum_{i=1}^4 w_i)$$

where $\hat{\theta}_i$ is the response rate difference of the i^{th} stratum and $w_i = 1/\text{var}(\hat{\theta}_i)$.

7.5.2.1 Subset Analyses of Objective Response

The influence of baseline and demographic characteristics on the treatment effect will be explored via exploratory subset analysis. The subsets will be the same as those analyzed for PFS.

The odds ratio and corresponding 95% CI will be presented for each subgroup in a forest plot.

7.5.2.2 Time to Tumor Response and Duration of Response

The analyses of duration of response will be conducted using the same censoring rules as used in the primary definition of PFS. The distribution of duration of response will be estimated, by arm, using the KM product limit method. The KM estimates will be presented graphically and will present number of events, number of subjects involved, medians along with 95% CIs for the medians.

Time to first tumor response which does not involve censoring, will be summarized by treatment group, using descriptive statistics.

No p-values will be provided for those analyses.

A by-subject listing will be presented including treatment arm, duration of response, whether the subject was censored for duration of response, and, if so, the reason.

7.5.3 Analysis of Overall Survival

Overall survival is another secondary objective. It will be compared between arms using a stratified log-rank test procedure with a two-sided, $\alpha = 0.2$ level. The stratification factors will be the same as those used for the analyses of PFS and tumor response. The OS function for each randomized arm will be estimated using the Kaplan-Meier product-limit method. Median and two-sided 95% confidence intervals for median OS will be computed by randomized arm.

All analyses performed for PFS (detailed in [Section 7.5.1](#)) will be repeated for OS. Supportive analyses of PFS (detailed in [Section 7.5.1.1](#)) as well as the subset analyses (detailed in [Section 7.5.1.2](#)) will also be repeated for OS.

7.5.4 Currentness of PFS and OS Data

Time from last tumor assessment to data cut-off in months will be summarized by treatment arm and overall for all randomized subjects. Subjects who have a PFS event will be considered as current for this analysis. The primary (ITT) definition of PFS will be used for this summary.

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.

By-subject listings will also be produced to accompany the subject time from last tumor assessment table.

7.5.5 Efficacy Assessments

A by subject listing of efficacy will be provided to present the following:

- Percent change in serum and urine M-protein, from baseline and nadir.
- Serum free light chain kappa and lambda concentrations and the kappa/lambda ratio.
- Serum and urine immunofixation test results.
- Corrected calcium results
- Results of bone marrow analysis, including plasma cells (%) and clonality of plasma cells.
- Radiologic evaluation of extramedullary plasmacytoma and lytic bone lesions

In addition, a plot of the change in mean Serum and Urine M-protein per cycle will be presented.

7.6 Safety

Safety summaries will be based on the treated subject population, grouped by treatment regimen received. A subject's treatment regimen received will equal the arm to which the subject was assigned at randomization as long as he did not receive the wrong regimen throughout the study.

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 per subject within each SOC and preferred term, according to their worst CTC grade.

Tables will be sorted by SOC and preferred term, with SOCs ordered by decreasing frequency overall and then alphabetically. Preferred terms will be sorted within SOCs by descending frequency overall and then alphabetically. The sorting will be done based on the total column when arms are presented side-by-side.

The following summaries will be presented by treatment arm:

Frequency tables of the worst grade of on-study AE will be presented: one table with AEs broken out by individual grade (1, 2, 3, 4 or 5) and an Any Grade category and another table in which both arms are included and grades are grouped as follows "Any, Grade 3-4 and Grade 5." The last summary will be repeated for:

- On-study drug-related AEs.
- On-study AEs that occurred \leq Cycle 2 and \geq Cycle 3.

A by-subject listing of all AEs 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:

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

and will be displayed along with a count of events

For these additional tables, AEs can be counted multiple times within each SOC and preferred term.

A by-subject listing of unique AEs will be provided.

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.
- Drug related AEs leading to discontinuation

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

7.6.3 Adverse Events of Special Interest

7.6.3.1 Infusion Reaction

Infusion reaction is a known elotuzumab toxicity. It will be based on investigator assessment and will be defined as any non-serious or serious adverse event judged by the investigator to be infusion related and which also occurs on the day of or the day after the elotuzumab infusion. These summaries will be presented:

- Frequency tables of the worst grade of on-study investigator infusion reaction (any grade and grade 1 through 5) by treatment group. The same summary will be presented with grades grouped as Any, Grade 3-4 and Grade 5.
- Frequency tables of the worst on-study investigator infusion reaction SAE will be also summarized by treatment group as above.
- Frequency of infusion reaction by infusion rate.
- Frequency of infusion reaction by elotuzumab concentration
- Frequency of infusion reaction by cycle.

By-subject listings of infusion reactions will be produced.

7.6.3.2 Opportunistic Infections

Multiple myeloma is associated with immune dysfunction and the natural course of the disease includes increased infection risk. In addition, elotuzumab may inhibit some cellular components of the immune system. Therefore, a thorough characterization of infections will be presented. Infections will be based on the SOC ‘infections and infestations’ and opportunistic infections will be based on clinically pre-defined PT terms ([Appendix 2](#)):

- Time to onset and duration of first infection
- Frequency of infections including opportunistic infections by treatment group.
- Absolute lymphocyte count at time of first infection
- Kinetics of lymphocyte reduction

7.6.3.3 Second Primary Malignancies

A summary table and a by-subject listing of second primary malignancies (SPM) will be provided. In addition, exposure-adjusted SPM incidence rates (including multiple occurrences of unique events) will be presented by treatment group and will be calculated as follows:

$$100 \times \frac{\text{Total number of unique SPM events}}{\left(\frac{\text{subject death date or last known alive date} - \text{subject date of first dose of study drug} + 1}{365.25} \right)}$$

Information on SPM will be obtained from the on-treatment eCRF page for secondary malignancies and the “Survival Status” eCRF page.

7.6.4 Safety in Subgroups

Summaries of all adverse events with $\geq 5\%$ frequency, adverse events leading to discontinuation, serious adverse events (any grade), and death within 60 days of last dose will be presented for the levels of the factors listed below.

In addition summaries by the same factors will be produced for second primary malignancies, opportunistic infections and infusion reactions.

- Age:
 - < 65
 - ≥ 65 up to < 75
 - ≥ 75 years
- Gender (male, female)
- Race (White, Black, Asian, Other)
- High risk vs. low risk vs. other standard

- Region (North America, Europe, Japan, and Rest of World)
- Number of prior lines of therapy (2-3 vs. ≥ 4)
- ECOG PS (0 vs. 1 or 2)

The sorting will be the same as for the overall table (not by subgroup).

7.6.5 Deaths

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

7.6.6 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, by treatment group. 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 treated subjects with on-study assessment for lab parameter. Subjects with a no 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: $\text{urea (mmol/L)} / 0.357 = \text{BUN (mg/dL)}$.

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 $> 2 \times$ ULN needs to be concomitant with or within 30 days after ALT or AST rising to $> 3 \times$ ULN. ALP needs to be $< 2 \times$ ULN at the time of or within 2 weeks before ALT or AST rising to $> 3 \times$ ULN or TBILI $> 2 \times$ ULN. This mean a normal ALP value ($\leq 2 \times$ 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. A separate listing will be provided for all subjects potentially experiencing DILI.

7.6.7 Echocardiogram, MUGA Scan and Electrocardiograms

A by subject listing of electrocardiogram (ECG) data collected at screening will be presented.

7.6.8 Vital Signs, Physical Measurements

Vital signs parameters (body temperature, seated diastolic and systolic blood pressure and heart rate) will be presented by visit and time point in a subject listing.

7.7 Pharmacokinetic Analysis

Elotuzumab concentrations taken pre (elotuzumab) dose and post-end of infusion, at each scheduled visit, will be summarized, by cycle and day, for subjects in the elotuzumab arm only. In addition to the standard summary statistics, the geometric mean and % CV will also be presented.

A by subject listing of elotuzumab concentrations will be provided.

7.8 Anti Drug Antibody Analysis

ADA status of a sample:

- Baseline ADA positive sample: ADA is detected in the last sample prior to the first dosing date/time of elotuzumab.
- On study ADA positive sample: after the first dosing date/time of elotuzumab:
 - ADA is detected in a subject whose baseline is negative
 - ADA is detected and ADA titer is at least 9-fold or greater (\geq) than the baseline positive ADA titers
- On study ADA negative sample: after the first dosing date/time of elotuzumab, no ADA detected relative to baseline or with a titer lower than the baseline sample.

Anti-drug antibody (ADA) will be summarized for elotuzumab arm only with the following categories:

- Baseline ADA Positive Subject: A subject with Baseline ADA Positive Sample

- **ADA Positive Subject:** A subject with at least one ADA positive sample after the first elotuzumab dose relative to baseline.
 - **Persistent Positive:** ADA positive sample at 2 or more sequential timepoints at least 3 months apart
 - **Only the Last Sample Positive:** ADA positive sample only in the last sampling timepoint.
 - **Other Positive:** not persistent positive with ADA negative sample in the last sampling
- **ADA Negative Subject:** A subject with no ADA positive sample after the first elotuzumab dose relative to baseline.

A by subject listing of all ADA data at each time-point will be provided along with corresponding elotuzumab concentration values measured as a part of pharmacokinetic assessments.

7.9 Pharmacogenomic Analysis

The relationship between elotuzumab effect on PFS and high risk cytogenetic abnormality will be explored through Cox regression modeling. The following analyses may be conducted depending on the number of subjects with available biomarker data in the trial. A separate model will be produced for each of the following FISH/cytogenetic abnormalities, which will be categorized as positive/negative:

- t(4:14)
- t(14:16)
- del 17p
- del(1q)
- del(1p)
- t(6:14)

Each model will contain treatment, FISH factor and a term for treatment by FISH/cytogenetic factor interaction. If treatment by FISH/cytogenetic factor interaction is not significant at the five percent level it will be excluded from the model. In addition, the treatment effect (median PFS along with corresponding HRs, and 95% CIs) may be computed separately, in the positive and negative groups. A similar analysis may be conducted to evaluate the effect on ORR using a logistic regression model.

Similar analyses, as described above, will be conducted to evaluate the relationship between baseline SLAMF7 expression on MM cells and NK cells with efficacy (PFS or ORR).

The level of SLAMF7 protein expression at baseline and at progression, and the change in SLAMF7 level, from baseline to progression, will be summarized, by arm, using descriptive statistics.

7.10 Health Related Quality of Life

The analyses of health related quality of life data will be conducted concurrently with the PFS analyses.

Two quality of life (QoL) questionnaires will be used: the M.D. Anderson Symptom Inventory Multiple Myeloma module MDASI-MM which measures symptoms, and the EuroQol Group's EQ-5D which measures utilities, and is a preference-based measure of health status.

The EQ 5D is a 5-item questionnaire and a “thermometer” visual analogue scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state) that will be administered at the same intervals as the other PRO instruments, including at the Screening Visit to assess the comparability of the groups at study initiation.

The MDASI-MM module is a valid instrument that asks patients to rate 13 symptoms (“core” items) and 6 symptom-related interference items that are common across cancer types and treatments. It also assesses 7 multiple myeloma-specific symptom items: bone aches, muscle weakness, sore mouth/throat, rash, difficulty concentrating, constipation, and diarrhea.

The key PRO endpoints to be included in the exploratory objectives are the pain, bone aches, and fatigue scores of the MDASI-MM scale in addition to the EQ-5D visual analog scale. The mean change in PRO scores between baseline and each post-baseline assessment will be summarized by treatment arm.

The remaining subscales of MDASI-MM and the EQ-5D summary index scores will also be tabulated.

It is possible that the QoL questionnaires are not completed in line with the visit schedule. An acceptable time delay or “window” during which the questionnaire must be completed is ± 1 week during treatment, at EOT, and the first two visits post treatment, to ensure evaluation of short-term toxicity and response. During follow up for EQ-5D, a wider window (± 3 weeks) would be acceptable after the first two post-treatment visits. A visit window will be assigned to the scheduled visits to ensure that each QoL questionnaire can be assigned to a scheduled visit; for each type of questionnaire the one closest to the schedule visit will be assigned.

For PROs, if a multi item subscale has a missing item, then the average of the remaining items will be used as the Scale score, as long as at least half the items in that Scale are present.

All analyses will be conducted on randomized subjects with baseline and at least one post-baseline assessment.

Descriptive statistics for each instrument will be provided at baseline.

For each instrument, the questionnaire completion rate will be defined as the proportion of questionnaires completed out of the expected number of questionnaires (i.e. the number of subjects randomized for baseline visit and still on treatment for post-baseline visits) at each assessment point (i.e. Screening, Day 1 of each cycle and End of treatment or study withdrawal). The questionnaire completion rate at each assessment point will be presented by treatment group.

By subject listings of the MDASI-MM and the EuroQol Group's EQ-5D data will be provided.

7.11 Healthcare Resource Utilization Data

A separate analysis plan will be developed for economic analyses that will be conducted from this trial. The economic analyses will combine the resource utilization data from the trial with data on unit prices (collected separately) to estimate total costs in preparation for a full-cost analysis.

8 CONVENTIONS

8.1 Baseline Definition

Baseline evaluations will be those performed within 60 days of randomization and 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.

Laboratory tests and procedures (ECG, physical measurement and 2D echocardiogram MUGA, skeletal survey and plasmacytoma) 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.

8.2 Age Definition

Age (years) will be calculated as:

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

8.3 Time Since Initial Diagnosis to Randomization Definition

Time from disease diagnosis to randomization (months) will be calculated as:

$$\frac{\text{date of randomization} - \text{date of initial diagnosis} + 1}{30.4375}$$

For the date of cancer diagnosis, the following conventions will be used for imputing partial dates:

- If only the day of the month is missing, the 15th of the month will be used to replace the missing day.
- If the day and month are missing or a date is completely missing, it will be considered as missing.

8.4 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.

8.5 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 1st of the month will be used to replace the missing day.
- If the day and month are missing or a date is completely missing, 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 1st 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 1st will be used to replace the missing information.

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

For partial dates of start of subsequent anti-myeloma therapy, the following conventions will be used:

- When the day is missing, the alternative therapy will be assumed to start on the first day of the given month if this day is later than the last dosing date. Otherwise the alternative therapy will be assumed to start on the day following the last dosing date.
- When the day and the month are missing, the alternative therapy will be assumed to start on the first day of the given year if this day is latter than the last dosing date. Otherwise the alternative therapy will be assumed to start on the day following the last dosing date.

8.6 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.

8.7 Topline Analyses

Outputs covering the following topics will be included in the top-line analyses:

Study conduct:

- Relevant eligibility deviations (Table and Listing)

Subject population:

- End of Treatment Summary
- Accrual by Region
- Accrual by stratification factors at randomization
- Demographic Characteristics Summary
- IVRS Stratification Factors Summary
- Baseline Myeloma Characteristics Summary (SI units)
- Other Baseline Laboratory Measurements Summary
- Risk Factors Results Summary
- Prior Systemic Anti-myeloma Therapy
- Prior Systemic Therapy Drugs Summary
- Refractory Status to Most Recent Line of Therapy Summary
- Time from Diagnosis to Randomization Summary
- Baseline Physical Measurements Summary

Extent of exposure:

- Number of Cycles Summary
- Elotuzumab Dose Intensity Summary
- Dexamethasone Dose Intensity Summary
- Pomalidomide Dose Intensity Summary
- Elotuzumab Delay Summary
- Elotuzumab Omission Summary
- Elotuzumab Infusion Interruption Summary
- Pomalidomide Reduction Summary
- Pomalidomide Interruption Summary

Tumor response:

- Best Overall Response
- Best Overall Response Odds Ratio and 95% CI in Subsets (Figure)

- Time to First Response Summary
- Kaplan-Meier Plot of Duration of Response

Progression free survival:

- Currentness of Follow-Up for PFS Summary
- PFS (ITT) Analysis
- Kaplan-Meier plot of PFS (ITT) (Figure)
- PFS (ITT) Analysis Adjusting for Different Baseline Covariates
- PFS (ITT) Hazard Ratio and 95% CI in Subsets (Forest plot)
- PFS (Secondary Def.) Analysis
- Kaplan-Meier plot of PFS (Secondary Def.) (Figure)
- PFS (Secondary Def.) Analysis Adjusting for Different Baseline Covariates
- PFS (Secondary Def.) Hazard Ratio and 95% CI in Subsets (Forest plot)

Overall survival:

- Currentness of Follow-Up for Overall Survival Summary
- Overall Survival Analysis
- Overall Survival Analysis Adjusting for Different Baseline Covariates
- Kaplan-Meier plot of overall survival (Figure)
- Overall survival Hazard Ratio and 95% CI in Subsets (Forest plot)

Safety:

- Hematologic Laboratory Test Results Summary of Worst Toxicity Grade - SI Units
- Renal and Liver Laboratory Test Results Summary of Worst Toxicity Grade - SI Units
- Chemistry Laboratory Test Results Summary of Worst Toxicity Grade - SI Units
- Other Laboratory Test Results Summary (BUN, DBILI, TPRO)
- Potential Drug Induced Liver Injury Cases Summary - SI Units
- Adverse Event Summary by CTC Grade Combined
- Related Adverse Event Summary by CTC Grade Combined
- Serious Adverse Event Summary by CTC Grade Combined
- Related Serious Adverse Event Summary by CTC Grade Combined
- Adverse Event Leading to Discontinuation Summary by CTC Grade Combined
- Related Adverse Event Leading to Discontinuation Summary by CTC Grade Combined
- Infusion Reaction Summary by Common Terminology Criteria
- Second Primary Malignancy Summary
- Deaths
- Deaths within 60 days of last study drug

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

[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

