Title: An Open-Label, Phase 2 Study to Evaluate the Oral Combination of MLN9708 with Cyclophosphamlde and Dexamethasone in.Patients with Newly Diagnosed Multiple Myeloma or Relapsed antVor Refractory Muμiple Myeloma Requiring Systemic Treatment

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SAP Approve Date: 22Aug 2016

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STATISTICAL ANALYSIS PLAN

An Open-Label, Phase 2 Study to Evaluate the Oral Combination of MLN9708 with Cyclophosphamide and Dexamethasone in Patients with Newly Diagnosed Multiple Myeloma or Relapsed and/or Refractory Multiple Myeloma Requiring Systemic Treatment

Protocol #: C16020 Amendment 1

SAP Version:	Date of Statistical Analysis Plan:
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Approval Signatures

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
5-HT_3	5-hydroxytryptamine 3 serotonin receptor
AE	adverse event
ALL	acute lymphoblastic leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myelogenous leukemia
ANC	absolute neutrophil count
API	active pharmaceutical ingredient
aPTT	activated partial thromboplastin time
Ara-C	Cytarabine
ASCO	American Society of Clinical Oncology
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
BCRP	breast cancer resistance protein
βhCG	beta-human chorionic gonadotropin
BID	bis in die; twice a day
BM	bone marrow
BSA	body surface area
BUN	blood urea nitrogen
BZD	Benzodiazepines
CBC	complete blood count
CFR	Code of Federal Regulations
C_{max}	single-dose maximum (peak) concentration
CNS	central nervous system
CO_2	carbon dioxide
CR	complete response
CRM	continual reassessment method
CRP	C-reactive protein
CSF-1R	colony-stimulating factor 1 receptor
CT	computed tomography
CV	coefficient of variation ***or*** cardiovascular *choose one*
CYP	cytochrome P_{450}
DLT	dose-limiting toxicity
DME	drug metabolizing enzymes
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
eCRF	electronic case report form
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EOS	End of Study (visit)
EOT	End of Treatment (visit)
EU	European Union
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GGT	gamma glutamyl transferase
GI	Gastrointestinal
GLP	Good Laboratory Practices
GM-CSF	granulocyte macrophage-colony stimulating factor
GMP	Good Manufacturing Practice
Hb	Hemoglobin
Hct	Hematocrit
HDPE	high-density polyethylene
HDT	high-dose therapy
hERG	human ether-à-go-go related gene
HIV	human immunodeficiency virus
HNSTD	highest nonseverely toxic dose
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IMiD	immunomodulating drugs
inc	Including
IR	Immunophenotype
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous; intravenously
IVRS	interactive voice response system
K_i	inhibition constant
KPS	Karnofsky Performance Status
LDH	lactate dehydrogenase
LFT	liver function test(s)
Ixazomib	Generic name of MLN9708

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MM	multiple myeloma
MRD	minimal residual disease
MRI	magnetic resonance imaging
MRU	medical resource utilization
MTD	maximum tolerated dose
MUGA	multiple gated acquisition (scan)
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDMM	newly diagnosed multiple myeloma
NPO	nothing by mouth
nCR	nearly complete response
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease (disease progression)
PFS	progression-free survival
Pgp	P-glycoprotein
PK	pharmacokinetic(s)
PN	peripheral neuropathy
PO	*per os*; by mouth (orally)
POEMS	polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes
PR	partial response
PRO	patient-reported outcome
PSA	prostate-specific antigen
QD	*quaque die*; each day; once daily
QID	*quater in die;* 4 times a day
QOD	*quaque altera die*; every other day
QOL	quality of life
QTc	rate-corrected QT interval (millisec) of electrocardiograph
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RRAL	relapsed and/or refractory systemic light chain amyloidosis
RRMM	refractory multiple myeloma
SAE	serious adverse event
SC	Subcutaneous

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
sCR	stringent complete response
SCT	stem cell transplant
SD	stable disease
SmPC	Summary of Product Characteristics
$t_{1/2}$	terminal disposition half-life
TGI	tumor growth inhibition
T_{max}	first time of occurrence of maximum (peak) concentration
TTP	time-to-progression
UK	United Kingdom
ULN	upper limit of the normal range
US	United States
VGPR	very good partial response
VMP	VELCADE to melphalan and prednisone
WBC	white blood cell
WHO	World Health Organization

1. INTRODUCTION

In general, the purpose of the statistical analysis plan (SAP) is to provide a framework that addresses the protocol objectives in a statistically rigorous fashion, with minimized bias or analytical deficiencies. Specifically, this plan has the following purpose:

To prospectively (a priori) outline the types of analyses and data presentations that will address the study objectives outlined in the protocol, and to explain in detail how the data will be handled and analyzed, adhering to commonly accepted standards and practices of biostatistical analysis in the pharmaceutical industry.

1.1 Study Design

This is an open-label, phase 2 study designed to evaluate the safety and efficacy of the combination of Ixazomib with cyclophosphamide (C) and dexamethasone (d) in patients with NDMM who have not received prior systemic treatment for multiple myeloma (MM) and are ineligible for high-dose therapy (HDT)-stem cell transplantation (SCT) due to age or comorbid disease(s), and in patients with RRMM who have received 1 to 3 lines of prior therapy and whose disease is not refractory to proteasome inhibitors.

Patients with NDMM will receive Ixazomib in combination with Cd for an induction phase up to approximately 1 year (13 × 28-day cycles) and, if at least stable disease has been reached with an acceptable toxicity profile after induction, patients will be administered, as maintenance, single-agent Ixazomib (at the dose tolerated at the end of induction) in 28-day treatment cycles until progressive disease (PD), death or unacceptable toxicity. Patients will be randomized 1:1 to either Arm A or Arm B, which have different doses of cyclophosphamide during induction period. During induction phase, each 28-day treatment cycle consists of oral Ixazomib(4.0 mg on Days 1, 8, and 15) administered in combination with cyclophosphamide (300 mg/m^2 [Arm A] OR 400 mg/m^2 [Arm B] both on Days 1, 8, and 15) and dexamethasone (40 mg on Days 1, 8, 15, and 22) all administered orally. Patients over 75 years of age will receive a reduced dose of dexamethasone 20 mg on the same weekly schedule. During maintenance phase, each 28-day treatment cycle consists of single agent oral Ixazomib(4.0 mg on Days 1, 8, and 15).

Patients with RRMM (Arm C) will receive Ixazomib 4.0 mg weekly on Days 1, 8, and 15, in combination with cyclophosphamide 300 mg/m^2 on Days 1, 8, and 15, and dexamethasone 40 mg on Days 1, 8, 15, and 22 of a 28-day cycle (all orally administered). Patients over

75 years of age will receive a reduced dose of dexamethasone 20 mg on the same weekly schedule. Patients with RRMM will be enrolled to Arm C and treated until disease progression, death or unacceptable toxicity. No maintenance phase is planned for Arm C.

For all three treatment arms, a safety lead-in evaluation will be performed after at least 6 patients in each treatment arm have had the opportunity to complete at least 1 cycle of therapy. DLTs observed in the first 6 patients in this treatment arm will be used to determine the safety and overall tolerability of the study regimen and the feasibility of continued recruitment of patients to the study.

Patients will attend an End-of-Treatment (EOT) visit approximately 30 days after receiving their last dose of study drug. Patients who stop treatment for any reason other than PD will continue to have PFS follow-up visits. The PFS follow-up visits should occur every 8 weeks from EOT until the occurrence of PD or death, the patient withdraws consent for further follow-up, whichever comes first.

The study will be conducted to fully characterize the safety, tolerability, efficacy, quality of life (QOL), and the pharmacokinetics (PK) of Ixazomib.

1.2 Study Objectives

1.2.1 Primary Objectives

The primary objective for patients with newly diagnosed multiple myeloma (NDMM) is:

- To determine the combined response rate of complete response (CR) (including stringent CR [sCR]) + very good partial response (VGPR) following treatment of oral Ixazomib when added to a standard regimen of cyclophosphamide and low-dose dexamethasone (Cd) during the induction phase.

The primary objective for patients with relapsed and/or refractory multiple myeloma (RRMM) is:

- To determine overall response rate (ORR; CR + VGPR +partial response [PR]), following treatment with oral Ixazomib when added to a regimen of Cd.

1.2.2 Secondary Objectives

For patients with NDMM, the secondary objectives are:

- To evaluate the tolerability and toxicity of the combination of oral Ixazomib with Cd
- To characterize the PK in plasma of oral Ixazomib in combination with Cd
- To determine overall response rate (ORR; CR + VGPR + PR), CR, VGPR, and PR during the induction phase and the ORR (CR + VGPR + PR), CR + VGPR, CR, VGPR, and PR throughout the entire treatment period
- To determine time to response for patients who respond during the induction phase
- To determine duration of response (DOR) for patients who respond during the induction phase
- To determine time to progression(TTP)
- To evaluate PFS
- To describe the safety, tolerability, and efficacy of Ixazomib as maintenance therapy in patients who continue treatment beyond 13 cycles of induction therapy
- To assess change in global health status, as measured by the patient-reported outcome (PRO) instrument: European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30).

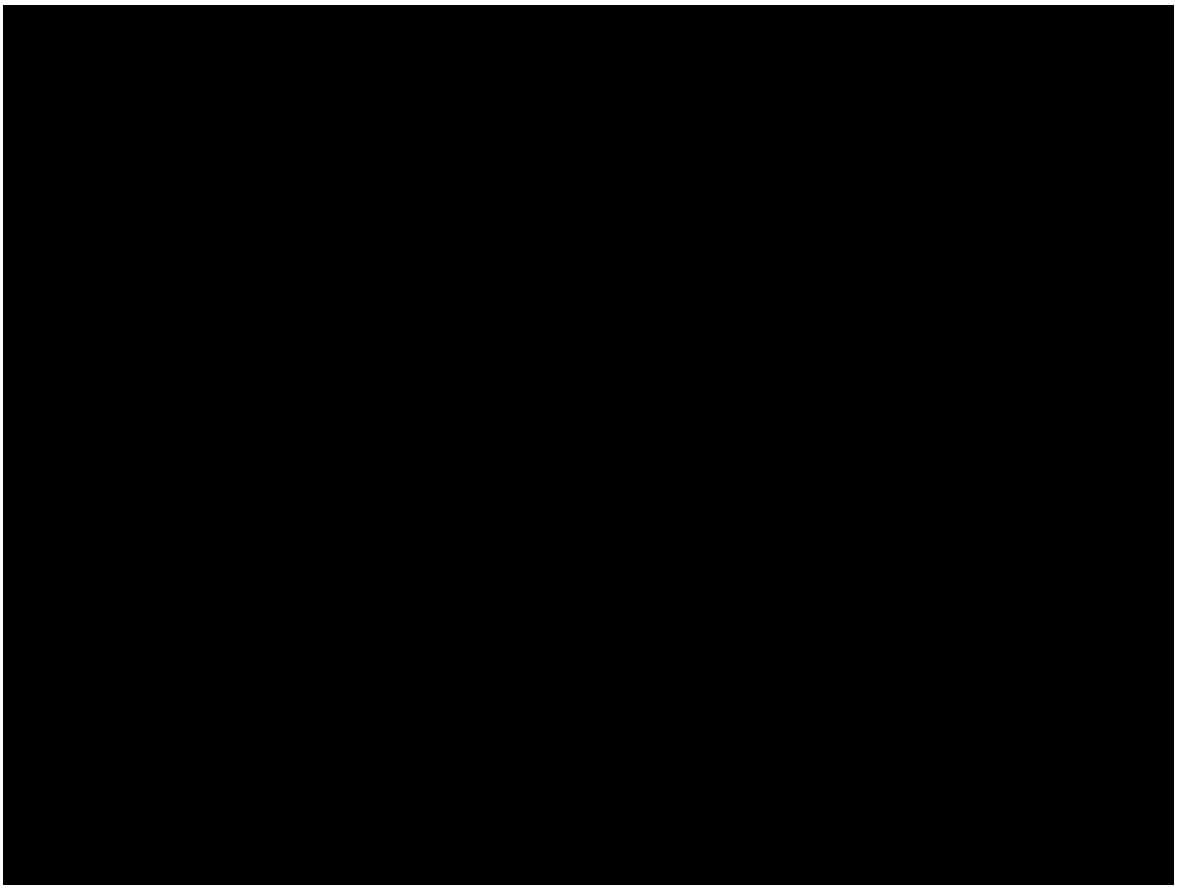
For patients with RRMM, the secondary objectives are:

- To evaluate the tolerability and toxicity of the combination of oral Ixazomib with Cd
- To characterize the PK in plasma of oral Ixazomib in combination with Cd
- To determine CR + VGPR, CR, VGPR, and PR
- To determine time to response for patients who respond
- To determine DOR
- To determine TTP
- To evaluate PFS

- To assess change in global health status, as measured by the patient-reported outcome (PRO) instrument: European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30).

1.2.3 **Exploratory Objectives**

The exploratory objectives are:



2. POPULATIONS FOR ANALYSIS

2.1 Safety Population

The safety population is defined as all patients who receive at least 1 dose of any study drug. Patients will be analyzed according to the treatment arm actually received. The safety population will be used for safety related analyses such as AE, concomitant medication, laboratory tests, and vital signs. In addition, it will also be used for the analyses of TTP, PFS and QOL data.

2.2 DLT-Evaluable Population

The DLT-Evaluable population is defined as patients in the safety lead-in cohort who receive all doses of Ixazomib and at least 80% of cyclophosphamide during Cycle 1 or experience a DLT in Cycle 1. Patients must take all doses in Cycle 1 as outlined in the Schedule of Events if patients do not experience DLTs. The DLT-Evaluable population will be used to evaluate the toxicity and determine a tolerable dose and dose modification following Cycle I of safety lead-in.

2.3 Response-Evaluable Population

The response evaluable population is defined as patients who receive at least 2 of the 3 Ixazomib doses during Cycle 1, have measureable disease at baseline, and at least 1 post-baseline response assessment. The response-evaluable population will be used for the analyses of response rates (RR), time to response (TTR), and duration of response (DOR). Measurable disease is defined by the documentation of at least 1 of the following 3 measurements:

- Serum M-protein ≥ 1 g/dL (≥ 10 g/L).
- Urine M-protein ≥ 200 mg/24 hours.
- Serum free light chain (FLC) assay: involved free light chain level ≥ 10 mg/dL (≥ 100 mg/L) provided the serum free light chain ratio is abnormal.

2.4 Pharmacokinetic Analysis Population

The Pharmacokinetic analysis population is defined as all patients who are enrolled in the safety lead-in cohort and have sufficient dosing data and Ixazomib concentration-time data to permit calculation of Ixazomib pharmacokinetic parameters.

3. HYPOTHESES AND DECISION RULES

For patients with NDMM, the null hypothesis is that the combined CR+VGPR rate is not different in the treatment arms of Ixazomib in combination with cyclophosphamide and low-dose dexamethasone from the specified response rate based on historical control, i.e.,

$$H_0: \text{CR+VGPR rate} = 27\%$$

The alternative hypothesis is that Clinical response rate in the treatment arm is different from that of historical control, i.e.,

H_A: CR+VGPR rate > 27%

For patients with RRMM, the null hypothesis is that the overall response rate (ORR: CR + VGPR + partial response [PR]) is not different in the treatment arm of Ixazomib in combination with cyclophosphamide and low-dose dexamethasone from the specified response rate based on historical control, i.e.,

H_0: CR+VGPR+PR rate = 60%

The alternative hypothesis is that Clinical response rate in the treatment arm is different from that of historical control, i.e.,

H_A: CR+VGPR+PR rate > 60%

The one group chi-square test will be used to test the hypothesis at a type I error rate of 0.10 (one - sided).

4. INTERIM ANALYSIS

4.1 Safety Lead-in Evaluation

A safety lead-in evaluation will be performed after at least 6 safety lead-in evaluable patients in each treatment arm have had the opportunity to complete 1 cycle of therapy. No formal statistical analysis is planned for the safety lead-in evaluation.

4.2 Continuous Monitoring and Early Stopping Rule

There is no formal interim analysis planned. Continuous data monitoring regarding safety and efficacy will be conducted based on the Bayesian monitoring strategy. Two proportions will be calculated for each arm: P_F, the proportion of patients who are considered an effectiveness success, and P_S, the proportion of patients who experienced one or more Grade 4 or higher non-hematological toxicities. P_F will be evaluated on the first 12 response-evaluable patients and then every 6 additional response-evaluable patients; P_S will be evaluated on the first 12 enrolled patients and then every 6 enrolled patients.

If the stopping bounds of Ps≥ 4/12, Ps≥ 6/18, Ps≥ 7/24, and Ps≥ 8/30 for Arms A and B (patients with NDMM), or the stopping bounds of Ps≥ 4/12, Ps ≥ 6/18, Ps≥ 7/24, Ps≥ 8/30, Ps≥ 9/36, Ps≥ 11/42, Ps≥ 12/48, Ps≥ 13/54, Ps≥ 14/60, Ps≥ 15/66, and Ps≥ 16/72 for Arm C (patients with RRMM) have been achieved, accrual to the study will be suspended to allow for investigation. If the stopping rule is met, there is at least 80% probability that the true

toxicity rate will be greater than 18%. After consideration by the study team, a decision will be made as to whether accrual can be resumed.

If the futility stopping bounds (CR + VGPR) of $P_F \leq 2/12$, $P_F \leq 4/18$, $P_F \leq 7/24$, and $P_F \leq 10/30$ for Arms A and B, or the futility stopping bounds (ORR) of $P_F \leq 5/12$, $P_F \leq 12/24$, $P_F \leq 20/36$, $P_F \leq 29/48$, and $P_F \leq 37/60$ for Arm C have been met, further investigation will be made by the study team to assess if accrual to any of the 3 treatment arms may be terminated due to futility. These futility stopping rules are established to allow no larger than 10% overall type I error rate (one-sided) and still maintain power of approximately 80%.

5. STATISTICAL METHODOLOGY

In general, summary tabulations will be presented to display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percentage (of nonmissing) per category for categorical data, unless specified otherwise. Patients will be analyzed at the dose level to which they were originally assigned, unless specified otherwise, including those who receive subsequent treatment at a lower dose level or a higher dose level. Tables will be summarized by treatment arms.

At the time of clinical study report(CSR) lock, all relevant data will be queried and cleaned; a database snapshot will be taken and used for the CSR. Additional treatment data will be entered into the database through study termination. Analyses may be updated based on additional information. An addendum to the CSR may be written if warranted based on these analyses.

5.1 Sample Size Justification

This is a 3-arm open-label, multicenter, phase 2 study designed to evaluate the efficacy and safety of the oral combination of Ixazomib with cyclophophamide and dexamethasone in patients with NDMM (Arm A or Arm B) or patients with RRMM (Arm C).

For patients with NDMM(Arm A or Arm B), the sample size is calculated by using one group chi-square test for each arm separately based on the CR + VGPR rate following Ixazomib combined treatment regimen. With 31 response-evaluable patients per treatment arm (Arm A or Arm B), there will be 80% power to test a null hypothesis CR + VGPR rate of 27% and an alternative hypothesis CR + VGPR rate of 45% at 1-sided significant level of $\alpha = 0.10$. Assuming 10% patients are not response evaluable, approximately 35 patients each (70 total) will be enrolled in these 2 treatment arms (Arm A and Arm B).

For patients with RRMM (Arm C), the sample size is calculated by using one group chi-square test based on the ORR rate following a Ixazomib combined treatment regimen. With 71 response-evaluable patients in Arm C, there will be 80% power to test a null hypothesis ORR rate of 60% and an alternative hypothesis ORR rate of 72% at 1-sided significant level of $\alpha = 0.10$. Assuming 10% patients are not response evaluable, approximately 78 patients will be enrolled in Arm C.

Overall, approximately 148 patients will be enrolled in this study.

5.2 Randomization and Stratification

For patients with NDMM (Arm A or Arm B), a central (not center specific) randomization scheme will be used. Eligible patients will be randomized to Arm A or Arm B at a ratio of 1:1. A randomization number will be assigned to each patient. The randomization assignment will be implemented by an interactive web response system (IWRS). Randomization is not required if accrual to either Arm A or Arm B is stopped, and therefore the enrollment can remain open for the other arm.

For patients with RRMM (Arm C), randomization will not be used but an IWRS will be implemented for enrollment.

5.3 Unblinding

This is an open-label study. No unblinding methodology is required.

5.4 Data Handling

5.4.1 Methods for Handling Missing Data

All available efficacy and safety data will be included in data listings and tabulations. Data that are potentially spurious or erroneous will be examined under the auspices of standard data management operating procedures. No imputation of missing data will be performed unless specified.

5.4.1.1 Missing Data in Patient Reported Outcomes (PROs)

For PRO data, missing data imputation will be based on published instrument specific methods.

For QOL in EORTC QLQ-C30, 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. Example: for fatigue, if Item 12 is missing, the average score of Items 10 and 18 will be used.

5.4.1.2 Missing/Partial Dates in Screening Visit

The following rules apply to dates recorded during the screening visits.

1. If only the day-component is missing, the first day of the month will be used if the year and the month are the same as those for the first dose of study drug. Otherwise, the 15th will be used.

2. If only the year is present, and it is the same as the year of the first dose of study drug, the 15th of January will be used unless it is later than the first dose, in which case the date of the first of January will be used.

3. If only a year is present, and it is not the same as the year of the first dose of study drug, the 15th of June will be used, unless other data indicate that the date is earlier.

5.4.1.3 Missing/Partial Dates in Adverse Events/Concomitant Therapies/Subsequent Therapies

5.4.1.3.1 Missing/Partial Dates in Adverse Events

Adverse events with stop dates that are completely or partially missing will be imputed as follows:

1 If the stop date has month and year but day is missing, the last day of the month will be imputed

2 If the stop date has year, but day and month are missing, the 31th of December will be imputed

After the imputation, the imputed dates will be compared against the date of death, if available. If the imputed date is later than the date of death, the date of death will be used as the imputed date instead. If the stop date of an adverse event is completely missing, then this event will be regarded as ongoing and will be included in the summary table.

Adverse events with start dates that are completely or partially missing will be imputed as follows:

1. If the start date has month and year but day is missing

a. If the onset month and year are same as that of first dose date, the first dose date will be used instead. If the onset month and year are different from that of the first dose date, then the first day of the month will be used.

b. After imputation, the imputed dates will be compared against the stop date. If this imputed date is later than the stop date (possibly imputed), then the stop date will be used instead

2. If the start date has year, but day and month are missing

a. If the onset year is same as that of first dose date, then the first dose date will be used instead

b. If onset year is different than that of the first dose date, the 1st of January of the year will be imputed.

c. After the imputation, the imputed dates will be compared against the dose stop date. If this imputed date is later than the stop date (possibly imputed), then the stop date will be used instead.

If the start date of an adverse event is completely missing, then it is imputed with the first dose date.

5.4.1.3.2 Missing/Partial Dates in Concomitant Therapies

Concomitant therapies with start dates that are completely or partially missing will be analyzed as follows:

1. If the start date has month and year but day is missing, the therapy will be included in the summary table if the month and year are:

a. On or after the month and year of the date of the first dose of study drug

and

b. On or before the month and year of the date of the last dose of study drug plus 30 days.

2. If the start date has year, but day and month are missing, the therapy will be included in the summary table if the year is:

a. On or after the year of the date of the first dose of study drug

   and

b. On or before the year of the date of the last dose of study drug plus 30 days.

If the start date of concomitant therapies is completely missing and the stop date of concomitant therapies is prior to the date of the first dose of study drug, then this therapy will not be included.

If the start date of concomitant therapies is completely missing and the stop date of concomitant therapies is on or after the date of the first dose of study drug, then the therapy will be included in the summary table.

If the start date and stop date of concomitant therapies are completely missing, then the therapy will be included in the summary table.

5.4.1.3.3 Missing/Partial Dates in Subsequent Therapies

Subsequent therapies with start dates that are completely or partially missing will be analyzed as follows:

1. When month and year are present and the day is missing,

   a. If the onset month and year are the same as the month and year of last dose of study drug, the day of last dose + 1 will be imputed.

   b. If the onset month and year are not the same as the month and year of last dose of study drug, the first day of the month is imputed.

2. When only a year is present,

   a. If the onset year is the same as the year of last dose of study drug, the date of last dose + 1 will be imputed.

   b. If the onset year is not the same as the year of last dose of study drug, the first day of the year is imputed.

If no components of the onset date are present the date of last dose + 1 will be imputed.

5.4.2 Definition of Baseline Values

In general, the baseline value is defined as the value collected at the time closest to, but prior to, the first dose of study drug on Day 1 of Cycle 1. For example, this applies to most of safety chemistry and hematology labs.

However, for certain efficacy related labs (serum and urine M-protein, free light chain, response biomarkers etc), baseline is defined as the worst value (usually highest but could be lowest in some cases for certain biomarkers) from central labs (both scheduled and unscheduled) prior to first dosing. If all central labs are missing, then the worst value obtained from local lab (both scheduled and unscheduled) will be used. Please note that decisions regarding eligibility (such as response evaluable) may be made using either local or central laboratory.

5.4.3 Windowing of Visits

All data will be categorized based on the scheduled visit at which they were collected. These visit designators are predefined values that appear as part of the visit tab in the eCRF.

5.4.4 Justification of Pooling

All data from all sites will be pooled. Study center or treatment-by-center interaction will not be included in any statistical analysis.

5.4.5 Withdrawals, Dropouts, Lost to Follow-up

Time to event parameters will be censored if patients withdraw, drop out, or are lost to follow-up before documentation of the events (progressive disease /death). Rules for censoring are detailed in section 5.8.2.

5.4.6 General Conventions for Determining Duration

The duration of an event is calculated as: date of end of the event – date of start of the event +1. It shall be used for deriving the duration form a reference time point, e.g., days on treatment = date of last dose- date – date of first dose +1 and for time to event analyses such as survival or time to tumor progression. Table, listing, figure (TLF) shells will specify if there are exceptions.

5.5 Patient Disposition

The disposition of patients includes the number and percentage of patients for the following categories: patients in each of the study population, patients discontinued from the treatment regimen, primary reason for discontinuation from the treatment regimen, patients ongoing in follow-up, patients off study during follow-up and primary reason off study during follow-up. Percentages will be presented for each arm and the total of Arm A + Arm B. Patient disposition will be summarized and listed. The number and percentage of patients discontinued from the treatment regimen, primary reason for discontinuation from the treatment regimen will also be summarized for induction phase and maintenance phase separately for Arm A, Arm B and the total of Arm A + Arm B.

5.6 Demographics and Baseline Characteristics

5.6.1 Demographics

Demographic data will be summarized by each treatment arm and by the total of Arm A + Arm B. Baseline demographic data to be evaluated include gender, age, race, ethnicity, height, weight, body surface area (BSA), and other parameters as appropriate. No inferential statistics will be carried out.

Age will be calculated from date of birth and date of informed consent.

The formulation for BSA (Mosteller, 1987) is:

$$BSA = \text{sqrt}(\text{height(cm)} \times \text{weight (kg)} / 3600).$$

5.6.2 Disease Specific History

Disease specific history will be summarized to include type of myeloma at diagnosis, Durie-Salmon stage at diagnosis, International Stage System (ISS) at diagnosis, evidence of lytic bone disease and extramedullary disease, and the prior therapies for patients with RRMM (number of patients with prior therapy, lines of prior therapies, best hematological response to prior therapy, type of prior therapy in the format of therapy contained, number of patients who received VELCADE as the last line of prior therapy, number of patients refractory to any line of prior therapy). Disease specific history will be summarized and listed by each treatment arm and by the total of Arm A + Arm B. The months from prior diagnosis to the first dose of ixazomibis calculated by

$$\frac{\text{first dose date - date of diagnosis}}{365.25/12}$$

5.6.3 Baseline Disease Characteristics

Baseline disease characteristics will be summarized by each treatment arm and the total of Arm A + Arm B including serum M-protein, urine M-protein, serum free light chain, serum free light chain ratio, β_2-microglobin and its category (i.e., < 2.5, 2.5-5.5, > 5.5 mg/L), serum creatinine and its category, (<=2, >2 mg/dL), calculated creatinine clearance and its category (<30, 30-<60, 60-<90, >=90 mL/min), serum albumin by category (i.e., <3.5, >=3.5 g/dL), corrected calcium, hemoglobin, platelet count, neutrophil count, LDH and Eastern Cooperative Oncology Group (ECOG) performance status.

Creatinine clearance will be calculated using the Cockcroft-Gault formulas as follows:

For male patients:

$$\text{creatinine clearance} = \frac{(140 - \text{Age[yrs]}) \times \text{weight[kg]}}{72 \times (\text{serum creatinine[mg/dL]})}$$

For female patients:

$$\text{creatinine clearance} = 0.85 \times \frac{(140 - \text{Age[yrs]}) \times \text{weight[kg]}}{72 \times (\text{serum creatinine[mg/dL]})}$$

Integer values will be used.

For patients with heavy chain, the patient's type of myeloma is determined by the combination of heavy chain type (IgG, IgA, IgM, IgD, and other) and light chain type (Kappa, Lambda, and biclonal). In descriptive summaries, the disease will be categorized by the heavy chain type first, then within each of these categories, patients will be further classified according to their light chain type. For patients with light chain only, patients will be classified according to their light chain type.

5.6.4 Extent of Disease and Bone Marrow Cytogenetic Results at Baseline

The extent of disease at baseline will be summarized including number of patients with a bone marrow aspirate, bone marrow aspirate results (% plasma cells, % megakaryocytes

present), number of patients with a bone marrow biopsy, bone marrow biopsy results (% plasma cells, % cellularity, type of cellularity, % Kappa/Lambda ratio performed), skeletal survey results (normal, abnormal not clinically significant, abnormal clinically significant, and not done) and imaging including magnetic resonance imaging (MRI) / computed tomography (CT) results (normal, abnormal not clinically significant, abnormal clinically significant, and not done), number and percentage of lytic bone lesions present, number of extramedullary plasmacytoma present, and type of extramedullary plasmacytoma.

Bone marrow cytogenetic results at baseline from the conventional/karyotype and molecular/FISH cytogenetic analyses methods will be displayed. The results will be categorized as "Normal", "Abnormal" and "Indeterminate". The percentage of each category will be summarized. Abnormal types of interest, including but not limited to, del 13, del 17, t(4;14), t(11;14), t(14;16), -13q, -17p, hyperdiploidy, hypodiploidy and high risk cytogenetics group (del 17, -17p, t(4,14) or t(14,16)), will also be tabulated.

By-patient listings for these baseline characteristics will also be presented.

5.6.5 General Medical History

General medical history data will be presented in a by-patient listing.

5.7 Treatments and Medications

5.7.1 Concomitant Medications and Procedures

Concomitant medications will be coded by generic term using the World Health Organization (WHO) Drug Dictionary. The number and percentage of patients taking concomitant medications will be tabulated by WHO drug generic term from the first dose of study treatment through 30 days after the last dose of study medication. Concomitant procedures will not be coded.

Concomitant medications and procedures will be presented in by-patient listings.

5.7.2 Study Treatments

Eligible patients will take Ixazomib in combination with Cd. Patients with NDMM will be randomized to either to Arm A or Arm B. Patients with RRMM will be enrolled in Arm C.

During induction, patients with NDMM will be randomized to receive a combination of oral Ixazomib at a dose of 4.0 mg and a dose of cyclophosphamide at 300 mg/m^2 (Arm A) or 400

mg/m^2 (Arm B) on days 1, 8 and 15 of a 28-day cycle and dose of 40 mg of dexamethasone on Days 1, 8, 15, and 22 of a 28-day cycle; patients with RRMM will receive a combination of oral Ixazomib at a dose of 4.0 mg and a dose of cyclophosphamide at 300 mg/m^2 on days 1, 8 and 15 of a 28-day cycle and a dose of 40 mg of dexamethasone on Days 1, 8, 15, and 22 of a 28-day cycle. Patients over 75 years of age will receive a reduced dose of dexamethasone 20 mg on the same weekly schedule.

At the end of the induction phase, a maintenance phase starts for patients with NDMM (Arms A and B only) who have at least stable disease. Patients will receive single-agent Ixazomib (at the dose tolerated at the end of induction phase) on Days 1, 8, 15 of 28-day cycles until progression/death or unacceptable toxicity.

5.7.2.1 Extent of Exposure

A patient will be considered as treated in a cycle as long as this patient received any amount of study drug in that cycle. A treatment cycle is defined as a cycle in which the patient received any amount of study drug. A treatment cycle for a specific drug is defined as a cycle in which the patient received any amount of that drug.

Relative dose intensity (%) is defined as 100 × (total amount of dose taken (mg)) / (sum of the planned dose over all treatment cycles).

The exposure to each study drug will be summarized including the number of cycles, total amount of dose taken (in mg), total number of doses taken, number and percentages of patients by treatment cycles, and relative dose intensity. An aggregate summary of numbers and percentages of patients who had 1-6, 7-13, 14-20, 21-26, >26 treatment cycles will also be presented in the same table.

Exposure of Ixazomib will be presented by overall treatment period, induction period (Arms A and B only), and maintenance period (Arms A and B only). The summary of each study drug exposure will be presented by each treatment arm and the total of (Arm A + Arm B) in a similar format.

Dosing data will also be presented in a by-patient listing.

5.7.2.2 Treatment Modifications

The actions for each study drug (dose reduction, held, missed, increased, delayed, discontinued permanently, etc) will be summarized for all patients, over all treatment

periods, and by each cycle for Cycle 1 though Cycle 13, aggregated for Cycles 1-6, 7-13 (for all drugs) and then for the remainder of cycles.

5.8 Efficacy Analyses

Response will be assessed according to the International Myeloma Working Group (IMWG) criteria for all patients at every cycle during the treatment period and subsequently every 8 weeks during the PFS follow-up period until disease progression or the patient is off the study. Other efficacy parameters including, but not limited to time to, time to response (TTR) and duration of response (DOR) will be presented in listings and summarized if appropriate. Summary of best M-Protein Response to treatment will also be presented.

Subgroup analysis by age, ISS stage, creatinine clearance, ASCT, lines of prior therapy (RRMM), etc may also be explored for some efficacy endpoints.

5.8.1 Primary Efficacy Endpoints

For patients with NDMM, the primary endpoint is the combined response rate of CR + VGPR during the induction phase. For patients with RRMM, the primary endpoint is ORR. The primary efficacy analysis will be based on the response-evaluable population. Estimates of CR + VGPR and ORR will be calculated with 2-sided 95% exact binomial confidence intervals.

5.8.2 Secondary Efficacy Endpoints

For patients with NDMM, secondary efficacy endpoints include ORR (CR + VGPR + PR), CR, VGPR, PR rate during the induction phase, and ORR (CR + VGPR + PR), combined response rate (CR + VGPR), VGPR, CR, PR throughout the entire treatment period; TTR, DOR for patients who respond during the induction phase, TTP, PFS throughout the entire treatment period.

For patients with RRMM, secondary efficacy endpoints include combined response rate (CR + VGPR), VGPR, CR, PR, TTR, DOR, TTP, PFS.

Time to response (TTR) is defined as the time from the date of first dose of study treatment to the date of the first documentation of a confirmed PR or better response up to the initiation of alternative therapy in a patient who responded.

DOR is defined as the time from the date of first documentation of a confirmed PR or better to the date of first documented PD up to the initiation of alternative therapy. Responders

without documentation of PD will be censored at the date of the last response assessment that is SD or better prior to the date of the initiation of alternative therapy. DOR will be categorized as CR+VGPR+PR, CR+VGPR, and CR.

TTP is defined as the time from the date of first dose of study treatment to the date of first documentation of PD. Patients without documentation of PD will be censored at the date of the last response assessment that is SD or better prior to the date of initiation of alternative therapy. Patients with no response assessment will be censored at the date of first dose.

PFS is defined as the time from the date of first dose of study treatment to the date of first documented PD or death. Patients without documentation of PD or death will be censored at the date of the last response assessment that is SD or better prior to the date of initiation of alternative therapy. Patients with no response assessment will be censored at the date of first dose.

Time-to-event data will be summarized by 25^{th}, 50^{th} (median), and 75^{th} percentiles with associated 2-sided 95% confidence intervals, as well as percent of censored observations.

The response rates, time to response, and DOR will be analyzed based on Response-Evaluable populations. TTP and PFS will be analyzed based on the safety population. The response rates will be analyzed similarly to the primary endpoint. DOR, TTP and PFS will be analyzed using standard survival analysis techniques based on Kaplan-Meier estimates. The efficacy results will be summarized for each treatment arm and for the total of Arm A and Arm B.

5.8.3 Exploratory Efficacy Endpoints Analysis

[redacted]

5.8.3.1 Minimal Residual Disease Analysis

[redacted]

[redacted]

5.8.3.2 Patient Reported Outcome Analysis (PRO)

Quality of Life will be assessed using the EORTC QLQ-C30 and analyses will be performed using the safety population for each treatment arm and the total of Arm A + Arm B. Descriptive statistics will be presented for the change from baseline in QOL assessment over time. For patients with NDMM who enter maintenance therapy after 13 cycles of induction treatment, descriptive statistics will be presented for the change from baseline and change from Cycle 13 in QOL assessment over time. Analyses will be performed on summary scores as well as subscale scores.

The scale/subscale scores of EORTC QLQ-C30 are defined as shown in Table 5-1. Primary subscales for analysis (with associated items in parenthesis) include Pain (items 9, 19), Fatigue (items 10, 12, 18), Physical functioning (items 1-5), and Global health status/QOL (items 29-30). Secondary subscales for analysis include Nausea/Vomiting (items 14-15), Dyspnea (item 8), Insomnia (item 11), Appetite loss (item 13), Constipation (item 16), Diarrhea (item 17), Financial difficulties (item 28), Role functioning (items 6-7), Cognitive functioning (items 20, 25), Emotional functioning (items 21-24), and Social functioning (items 26-27). QOL data will be reported for the responders (confirmed best response of CR+VGPR+PR) and non-responders to assess the QOL differences associated with disease response. In addition, PRO responder analyses by tumor responder groups will be performed, where PRO responders are defined as patients who improved by 10 points or more on the EORTC QLQ-C30 global health scale at any time post-baseline, and tumor responders are defined as CR+VGPR+PR, CR+VGPR, and CR respectively.

Published scoring manual and guidelines will be used to determine EORTC QLQ-C30 scale scores and handle missing data. Further investigation of missing patterns, imputation and subsequent sensitivity analyses may be conducted.

Table 5-1 Definition of Subscale Scores of EORTC QLQ-C30

Scale/Subscale	Individual Items
Physical functioning	1-5
Role functioning	6-7
Emotional functioning	21-24
Cognitive functioning	20, 25
Social functioning	26-27
Quality of life	29-30
Fatigue	10, 12, 18
Nausea and vomiting	14-15
Pain	9, 19
Dyspnea	8
Insomnia	11
Appetite loss	13
Constipation	16
Diarrhea	17
Financial difficulties	28

5.8.3.3 Efficacy Assessment as Maintenance Therapy

For patients with NDMM who enter maintenance therapy after 13 cycles of induction treatment, the efficacy of Ixazomib as maintenance therapy will be evaluated. The duration of maintenance therapy will be further explored. Additional efficacy endpoints include shift table for response categories, landmark analysis of PFS, and other efficacy endpoints if appropriate in the maintenance therapy portion of the study. For the efficacy endpoints above, the staring time point will be the first date of maintenance therapy.

5.8.3.4 Biomarker Analysis

[redacted]

5.9 Analysis of Health Care Utilization Data

Analyses of health care utilization data will be performed using the safety population and summarized for each treatment arm and by the total of Arm A + Arm B. In general, descriptive statistics of medical encounters (length of stay, inpatient, outpatient, and reason), and number of missing days from work or other activities by patient and caregiver will be presented.

5.10 Pharmacokinetic, Pharmacodynamic

5.10.1 Pharmacokinetic Analyses

The PK analysis population will be used for the description of the PK profile and for the calculation of PK parameters.

Safety Lead-in Cohort

PK evaluation will be based on concentrations of Ixazomib in specimens collected at pre-specified times prior to and following drug administration. Actual specimen collection times will be used for the calculation of PK parameters. In the event that actual collection times are either unreliable or missing, scheduled collection times will be used. For ease of presentation, scheduled collection times will be used to present results in tables and figures. Both scheduled and actual collection times will be presented in listings.

Concentrations of Ixazomib that are below the limit of quantification (BLQ) will be treated as zero. Concentration data that are considered anomalous may be excluded from the concentration summaries and plots and will not be used in the calculation of PK parameters. Evidence or explanations will be provided to justify the exclusion of data.

When summarizing concentrations or PK parameters, a minimum of 2 values are required to show the mean and geometric mean, and at least 3 values are required to show the standard deviation and coefficient of variation (CV).

Individual patient plasma concentration data will be listed. Concentrations will be summarized (N, mean, standard deviation, CV, geometric mean, median, minimum, and maximum) according to Arm (A, B, or C) and dosing cycle and day.

A semi-logarithmic plot of the mean plasma concentration-time curves of ixazomibfollowing Cycle 1, Day 1 dosing (pre-dose to 168 hours) and Cycle 1, Day 15 dosing (pre-dose to 336 hours) will be provided, respectively. Linear and semi-logarithmic

plots of the aggregate individual plasma concentration-time curves ("spaghetti" plots) of ixazomibfollowing Cycle 1, Day 1 dosing (pre-dose to 168 hours) and Cycle 1, Day 15 dosing (pre-dose to 336 hours), grouped according to Arm will be provided, respectively. In linear plots, a value of zero will be substituted for any BLQ values. In semi-logarithmic plots, BLQ values will be treated as missing.

Pharmacokinetic parameters will be calculated using non-compartmental analysis methods. The following PK parameters will be computed, as data permits, from concentration-time data:

Parameter	Definition	Units
C_{max}	Observed maximum concentration	ng/mL
T_{max}	First time C_{max} is observed	hr
AUC_{tau}	Area under the concentration-time curve from time 0 to the end of the dosing interval, estimated using the linear-log trapezoidal method	hr*ng/mL
λz	Terminal disposition phase rate constant	1/hr
$t_{1/2}$	Terminal disposition phase half-life	hr
Rac	Accumulation ratio	unitless

Different PK parameters will be calculated following dosing on Day 1and Day 15.

The PK parameters to be estimated for each day of dosing are as follows:

	Dosing Day	
PK Parameter	**1**	**15**
C_{max}	X	X
T_{max}	X	X
AUC_{tau} (tau = 168 hr)	X	X
λz		X
$t_{1/2}$		X
Rac		X

Individual patient parameter data will be listed. PK parameters will be summarized (N, arithmetic mean, standard deviation, CV, geometric mean, median, minimum, and maximum) according to Arm and dosing cycle and day.

All Patients

Concentration-time data from patients not in the safety lead-in cohort will be listed only.

Pharmacokinetic data collected for all patients including patients in the safety lead-in cohort of the study may be used to perform population PK analysis using a nonlinear mixed effects modeling approach to assess the effect of various demographic covariates on PK including data from other studies of Ixazomib, if possible.

5.10.2 Pharmacodynamic Analyses

Not applicable

5.11 Safety Analyses

Safety analysis will be performed using the safety population by each treatment arm or the total of Arm A + Arm B. Summary tabulations will be presented to display the frequency of incidence, intensity, type of AEs, ECGs, vital sign measurements, and clinical laboratory results.

For the lead in patients, the incidence of DLT will be listed.

5.11.1 Adverse Events

5.11.1.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be reported from the first dose of study drug through 30 days after administration of the last dose of study drug. All AEs will be presented in a by-patient listing. AEs will be tabulated according to the MedDRA by system organ class, high level terms and preferred terms. Treatment-emergent is defined as any AE that occurs after administration of the first dose of any study treatment through 30 days after the last dose of any study treatment.

Summary tabulations will include the following categories:

- Treatment-emergent AEs
- Drug-related treatment-emergent AEs

- Grade 3 or higher treatment-emergent AEs (also grade 3 only and 4 only will be reported seperately)
- Grade 3 or higher drug-related treatment-emergent AEs (also grade 3 only and 4 only will be reported separately)
- The most commonly reported treatment-emergent AEs (i.e., those events reported by > 10% of all patients)
- Serious adverse events
- Treatment-emergent AEs resulting in study drug reduction
- Treatment-emergent AEs resulting in any study drug discontinuation

For patients with NDMM who enter maintenance therapy after 13 cycles of induction treatment, AEs will be tabulated according to the MedDRA by system organ class, high level terms and preferred terms for induction phase and maintenance phase. Summary tabulations will include the following categories:

- Treatment-emergent AEs
- Grade 3 or higher treatment-emergent AEs
- Serious adverse events
- Treatment-emergent AEs resulting in study drug reduction
- Treatment-emergent AEs resulting in any study drug discontinuation

Patients with the same AE more than once will have that event counted only once within each body system, once within each high level term, and once within each preferred term.

Drug-related treatment-emergent AEs will also be summarized by the National Cancer Institute Common Toxicity Criteria (NCI CTCAE) version 4.03 AE[(1)]. Patients with the same AE more than once will have the maximum intensity of that event counted once within each body system, once within each high level term, and once within each preferred term.

Most commonly reported (at least 10% of all patients) treatment-emergent AEs will be presented by preferred term only. Patients with the same AE more than once will have that event counted only once within each preferred term.

An overall summary AE table will include numbers and percentages of patients who had any AE, drug-related AE, grade 3 or higher AE, grade 3 or higher drug-related AE, serious AE (SAE), drug-related SAE, AE resulting in any drug discontinuation, AE resulting in any dose reduction, AE resulting in any dose modification (defined as delay, reduction or discontinuation), and on-study deaths. On-study death is defined as the death that occurs between the first dose of study drug and up to 30 days after the last dose.

Additionally, by-patient listings of the AE of special interest will be presented including rash, peripheral neuropathies, thrombocytopenia, and gastrointestinal disorders, if appropriate.

5.11.1.2 Peripheral Neuropathy Events

[redacted]

[redacted]

5.11.1.3 Serious Adverse Events

The number and percentage of patients experiencing at least one treatment-emergent SAE will be summarized by MedDRA primary system organ class, high level term, and preferred term. Drug-related SAEs will be summarized similarly.

In addition, a by-patient listing of the SAEs will be presented (the listing will contain all SAEs regardless of treatment-emergent AE status).

5.11.1.4 Deaths

A by-patient listing of the on-study deaths will be presented. On-study death is defined as the death that occurs between the first dose of study drug up to 30 days after the last dose of study drug.

5.11.1.5 Adverse Events Resulting in Discontinuation of Study Drug

The number and percentage of patients experiencing at least one adverse event resulting in discontinuation of any study drug will be summarized by MedDRA system organ class, high level term, and preferred term.

A by-patient listing of treatment-emergent AEs resulting in discontinuation of any study drug will be presented. All AEs resulting in discontinuation of any study drug occurring on-study will be displayed.

5.11.1.6 Adverse Events Resulting in Dose Reduction

The number and percentage of patients experiencing at least one adverse event resulting in any dose reduction will be summarized by MedDRA system organ class, high level term, and preferred term.

A by-patient listing of AEs resulting in dose reduction of any study drug will be presented. All AEs resulting in dose reduction of any study drug occurring on-study will be displayed.

5.11.1.7 Dose Limiting Toxicities (DLTs)

A by-patient listing of DLTs that occur during Cycle 1 of treatment will be presented only for patients participating in the safety lead-in.

5.11.2 Laboratory Data

For the purposes of summarization in both the tables and listings, all laboratory values will be converted to standardized units. If a lab value is reported using a non-numeric qualifier (e.g., less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be used in the summary statistics, ignoring the non-numeric qualifier. However, for the bone marrow plasma cell percentage, the convention of (x-1)% (mainly for < 5% for CR) will be used.

Laboratory test results from the central laboratory will be used when they are available. Laboratory test results from local laboratories will be used only when no central laboratory test results exist at the same sample collection time point, unless specified otherwise.

Laboratory test results will be summarized according to the scheduled sample collection time point. Change from baseline will also be presented. The parameters to be analyzed include, but are not limited to:

- Hematology: hemoglobin, hematocrit, platelet count, leukocytes with differential,and neutrophils (absolute neutrophil count [ANC])

- Clinical chemistry: blood urea nitrogen, creatinine, total bilirubin, urate, lactate dehydrogenase (LDH), gamma glutamyl transferase (GGT), phosphate, albumin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), glucose, calcium, sodium, potassium, chloride, carbon dioxide (CO_2), and magnesium.

Shift tables the change in CTCAE grade will be constructed for hematology and chemistry laboratory parameters which have corresponding CTCAE grades to tabulate changes in NCI CTCAE (version 4.03)[(1)] from baseline to worst post baseline on study CTCAE grade. All the data from both scheduled and unscheduled time points are to be included in the shift table. However, at each time point, the central lab value is used preferentially. Only when the central lab value is not available will the local lab value be used

Worst changes from baseline for creatinine clearance will be tabulated and categorized by ≤ 30 mL/min and > 30 mL/min, and ≤ 60 mL/min and > 60 mL/min.

The mean and median estimates over time may be graphed for a selected list of lab parameters. These include but not limited to: LDH, creatinine, albumin, calcium, sodium, and phosphate from serum chemistry and WBC, absolute neutrophil count, hemoglobin, platelet count from hematology.

For patients with NDMM who enter maintenance therapy after 13 cycles of induction treatment, selected hematological parameters such as ANC, ALC, platelets, hemoglobin may be analyzed by induction phase and maintenance phase separately.

The box plots of creatinine, M-protein values, change of M-protein from baseline over time will be graphed as well. For mean/median figures over time and box plots over time, only the data from scheduled time points are included. At the same scheduled time point, if the central lab value is available, then it is used. Only if the central lab value is not available will the local lab value be used.

If appropriate, line graphs of individual tests over time will be used to show changes in laboratory measures over time for each individual patient. For figures showing the individual-patient lab values over time, all scheduled and unscheduled time points are included. At the same time point, if the central lab value is available, it is used; if not, the local lab value is used.

By-patient listings to be presented include hematology, clinical chemistry and urinalysis.

5.11.3 Vital Signs

The actual values of vital sign parameters including oral temperature, pulse rate, systolic and diastolic blood pressure, and weight, will be summarized over time for each treatment arm and the total of Arm A + Arm B. Change from baseline will also be presented. A by-patient listing will also be presented.

5.11.4 Electrocardiograms

ECGs, including abnormalities, will be listed in a by-patient listing.

QTc interval will be calculated using Bazett's correction and Fridericia's correction. The formulas are:

$$QTc\ (Bazett) = QT / (RR^{0.5})$$

$$QTc\ (Fridericia) = QT / (RR^{0.33})$$

where RR = 60 / heart rate (bpm)

5.11.5 Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group performance status over time will be summarized. Shifts from baseline to postbaseline over time will be summarized by treatment arm and the total of Arm A + Arm B.

5.11.6 Other Safety Assessments

Pregnancy testing results will be presented in a by-patient listing.

Additional safety analyses may be determined at any time to enumerate rates of toxicities and to further define the safety profile of the study drugs.

6. CHANGES TO PLANNED ANALYSES FROM PROTOCOL

There are no changes to the planned analyses from that described in the protocol.

Reference materials for this statistical plan include Clinical Study Protocol C16020 Amendment 1 (May 2014).

7. PROGRAMMING CONSIDERATIONS

7.1 Statistical Software

SAS version 9.2 (or higher) will be used for all analyses.

7.2 Rules and Definitions

Patient populations are defined in Section 2.

Baseline values are defined in Section 5.4.2.

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