Title: A Phase 2, Open-Label Study of Ixazomib+Daratumumab+Dexamethasone (IDd) in Patients with Relapsed and/or Refractory Multiple Myeloma (RRMM)

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STATISTICAL ANALYSIS PLAN

C16047

A Phase 2, Open-Label Study of Ixazomib+Daratumumab+Dexamethasone (IDd) in Patients with Relapsed and/or Refractory Multiple Myeloma (RRMM)

Protocol #: C16047

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1.1 Approval Signatures

Electronic signatures can be found on the last page of this document.

A Phase 2, Open-Label Study of Ixazomib+Daratumumab+Dexamethasone (IDd) in Patients with Relapsed and/or Refractory Multiple Myeloma (RRMM)

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3.0 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
CDF	cumulative distribution function
CFR	Code of Federal Regulations
C_{max}	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
CYP	cytochrome P_{450}
DLT	dose-limiting toxicity
DME	drug metabolizing enzymes
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	Electrocardiogram

Abbreviation	Term
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core Module 30
EORTC QLQ-MY20	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Multiple Myeloma Module 20
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-a-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)

Abbreviation	Term
Ixazomib	generic name of MLN9708
MID	minimally important difference
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
P-gp	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
sCR	stringent complete response

Abbreviation	Term
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

4.0 OBJECTIVES

4.1 Study Design

This is an open-label, multicenter, phase 2 study designed to evaluate the safety and efficacy of oral ixazomib in combination with daratumumab and dexamethasone in adult patients with MM who have received at least 1 prior therapy. All patients must have documented evidence of PD as defined by IMWG criteria on or after their last regimen.

The study treatment regimen is defined as the combination of ixazomib, daratumumab, and dexamethasone. All cycles are approximately 28 days with treatment given until PD or unacceptable toxicity. Ixazomib will be administered at 4 mg orally on Days 1, 8, and 15 of each 28-day cycle. In Cycle 1, ixazomib will be given after the daratumumab infusion; in subsequent cycles, if there have been no Grade 3 or higher infusion-related reactions (IRRs) in the previous cycle, ixazomib can be given prior to or at approximately the same time as the premedications that are administered prior to daratumumab infusion. Daratumumab will be administered intravenously at 16 mg/kg. Daratumumab will be given on Days 1, 8, 15, and 22 in Cycles 1 and 2; on days 1 and 15 in Cycles 3 to 6; on Day 1 in Cycles 7 and beyond. dexamethasone will be given weekly in split doses, ie, 20 mg the day before and after each daratumumab IV infusion.
At close/termination of the study, the patients still on ixazomib treatment will have the option to enroll in a separate open-label rollover study to continue receiving ixazomib if, in the opinion of the investigator and sponsor, that they have experienced a clinically important benefit from the ixazomib received in the study, have no alternative therapeutic option and would be harmed without continued access.

Patients will attend an End-of-Treatment (EOT) visit up to 30 days after receiving their last dose of study therapy. All study procedures outlined for the EOT visit will be completed as specified in the protocol. 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 4 weeks from EOT until the occurrence of PD or death, or the patient withdraws consent for further follow-up, whichever comes first. After PD occurs, the patient will enter into the OS follow-up period, in which the patient will be followed every 12 weeks until death or termination of the study.

The study will be conducted to evaluate the safety and efficacy of the study drug regimen and to evaluate treatment effects on patient-reported quality of life (QOL); PK data collected in this study will contribute to future population PK analyses of ixazomib. [redacted]

[redacted]

4.2 Study Objectives

4.2.1 Primary Objectives

The primary objective is to evaluate the proportions of patients with a response of VGPR or better to IDd treatment.

4.2.2 Secondary Objectives

The secondary objectives are:

- To measure PFS, TTP, and OS
- To measure ORR, time to response (TTR), and DOR
- To collect plasma concentration-time data for ixazomib to contribute to population PK analyses.
- To evaluate the safety/tolerability of IDd administered in a 28-day cycle.

4.2.3 Exploratory Objectives

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

5.0 ANALYSIS ENDPOINTS

5.1 Primary endpoints

The primary endpoint is the rate of VGPR or better response as evaluated by the investigator according to IMWG criteria, in patients that are response evaluable.

5.2 Secondary Endpoints

The secondary endpoints are:

- PFS, defined as the time from the date of first dose of any study drug treatment to the date of first documentation of progressive disease (PD) as evaluated by the investigator per IMWG criteria, or death due to any cause, whichever occurs first.
- TTP, defined as the time from the date of first dose of any study drug treatment to the date of first documented evidence of PD.
- OS, defined as the time from the date of first dose of any study drug treatment to the date of death.
- ORR (defined as CR, VGPR, plus partial response [PR], per IMWG criteria) during or after the study treatment, but before subsequent therapy or PD.
- TTR, defined as the time from the date of first dose of any study drug treatment to the date of first documented PR or better.
- DOR, measured as the time from the date of first documentation of PR or better to the date of first documented progression among those patients that responded.

5.3 Exploratory Endpoints

[redacted]

[redacted]

6.0 DETERMINATION OF SAMPLE SIZE

The statistical assumption is based on observed CR+VGPR rates in historical clinical studies with ixazomib[1], bortezomib[2], and daratumumab[3]. The sample size is calculated using the binomial exact test for single proportion based on the rate of VGPR or better of the IDd treatment regimen. With 54 response-evaluable patients, there will be 95% power to test a null hypothesis of a rate of VGPR or better of 30% and an alternative hypothesis of a rate of VGPR or better of 55% at 2-sided significance level of α=0.05. Therefore, assuming 10% of patients are not response-evaluable, the total enrollment will be approximately 60 patients.

7.0 METHODS OF ANALYSES AND PRESENTATION

7.1 General Principles

In general, summary tabulations will display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percentage per category for categorical data. The Kaplan-Meier survival curves and 25th, 50th (median), and 75th percentiles will be provided along with their 95% confidence intervals (CIs) for time-to-event data.

Baseline is defined as the value collected at the time closest to, but prior to, the start of any study drug administration, unless otherwise stated

All statistical analyses will be conducted using SAS® Version 9.4, or higher.

7.1.1 Study Definitions

7.1.2 Definition of study days

Study Day 1 is defined as the date on which a subject is administered their first dose of the medication. Other study days are defined relative to the Study Day 1 with Day 1 being Study Day 1 and Day -1 being the day prior to Study Day 1.

7.1.3 Definition of Study Visit Windows

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

7.1.4 Conventions for Missing Adverse Event Dates

Every effort will be made to avoid missing/partial dates in on-study data.

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

1. If the stop date has a month and year but the 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 date is later than the date of death, the date of death will be used as the imputed date instead.

Adverse events with start date completely or partially missing will be imputed as follows:

1. If the start date has month and year but day is missing, the first day of the month will be imputed.
    a. If this date is earlier than the first dose date, then the first dose date will be used.
    b. If this date is later than the stop date (possibly imputed), then the stop date will be used instead.
2. If the start date has a year, but day and month are missing, then 15th of June will be imputed.
    a. If this date is earlier than the first dose date, then the first dose date will be used instead.
    b. If this date is later than the stop date (possibly imputed), then the stop date will be used instead.
3. If the start date is completely missing then the first dose date will be used.

7.1.5 Conventions for Missing Concomitant Medication Dates

Every effort will be made to avoid missing/partial dates in on-study data.

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

1. If the start date has a month and year but the day is missing, the event will be considered concomitant if the month and year of the start date of the event 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 a year, but the day and month are missing, the event will be considered concomitant if the year of the start date of the event is:
    c. On or after the year of the date of the first dose of study drug

       and

    d. On or before the year of the date of the last dose of study drug plus 30 days
3. If the start date of an event is completely missing, then the event is assumed to be concomitant.

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

1. When month and year are present and the day of the month is missing,
    a. If the onset month and year are the same as the month and year of last dose with 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 with 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 with 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 with study drug, the first day of the year is imputed.

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

7.1.6 Conventions for Missing Initial Diagnosis Dates

1 If only day is missing but year and month are present, set day=15;

2 If only a 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 date, in which case the date of the first of January will be used, unless other data indicate that the date is earlier. 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.

3 If completely missing, set to null.

7.2 Populations for Analysis

7.2.1 Safety Population

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

7.2.2 Response-Evaluable Population

The response evaluable population is defined as patients who receive at least 1 dose of ixazomib, have measurable disease either during screening or prior to first dose of study drug and at least 1 post-baseline disease assessment. The response-evaluable population will be used for the analyses of primary endpoint, overall response rates (ORR), time to response (TTR), and duration of response (DOR). Measurable disease is defined by the documentation of at least 1 of the following 2 measurements:

- Serum M-protein ≥ 1 g/dL (≥ 10 g/L).
- Urine M-protein ≥ 200 mg/24 hours.

7.3 Disposition of Subjects

Patient disposition includes the number and percentage of patients for the following categories: patients discontinued from the treatment, primary reason to discontinue the treatment, patients discontinued from the study, and primary reason to discontinue from the study.

A listing will be generated to present patient disposition variables.

7.3.1 Significant Protocol Deviations

Significant protocol deviations will be presented by patient in a listing, which will include, but will not necessarily be limited to, the following:

- Any inclusion/exclusion criteria not met by an enrolled patient.
- Use of or administration of excluded and/or restricted medications, not in accordance with the study protocol.
- Study procedures not performed as per the clinical study protocol to the extent that the deviation may confound interpretation of primary clinical study objectives and/or affect patient safety.
- Dispensing of incorrect treatment and/or incorrect dose of clinical study medication.
- Any occasion that withdrawal criterion is met but the patient is not withdrawn.

Protocol deviations will be listed using the safety population. COVID-related deviation will be listed separately

7.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using safety population.

7.4.1 Demographic

Demographic data will be summarized using the safety set. Summaries will include age, age group (<65, >=65 - <75, >=75), sex, race, ethnicity, height, weight, and other parameters as appropriate. Age will be calculated from date of birth to date of informed consent.

7.4.2 Disease Specific History

Disease specific history (collected on the Disease Characteristics, Prior Therapy and Prior Radiation, Prior Transplant, and Prior Surgery CRF pages) will be summarized for all patients as appropriate, including type of myeloma at diagnosis (both heavy and light chain type), Durie-Salmon stage at diagnosis, International Stage System (ISS) at diagnosis, evidence of lytic bone disease and extramedullary disease, and the prior therapies (lines of prior therapies, best hematological response to prior therapy, type of prior therapy in the format of therapy contained, months from initial diagnosis to first dose of ixazomib). The months from prior diagnosis to the first dose of study drug is calculated as

$$\frac{\text{first dose date - date of diagnosis} + 1}{365.25/12}$$

7.4.3 Baseline Disease Characteristics

Baseline disease characteristics will be summarized, including type of myeloma at study entry, which will be derived using baseline measurements of laboratory data. These include serum M-protein, urine M-protein, serum free light chain (FLC), serum free light chain ratio, involved FLC, β_2-microglobin and its categories (i.e., < 3.5, 3.5-5.5, > 5.5 mg/L), serum creatinine and its categories, (<=2, >2 mg/dL), calculated creatinine clearance and its categories (<30, 30-<60, 60-<90, >=90 mL/min), serum albumin and its categories (i.e., <3.5, >=3.5 g/dL), corrected calcium, and Oncology Group (ECOG) performance status.

Corrected calcium is calculated as:

Serum calcium [mg/dL] + 0.8 x (4 - serum albumin [g/dL])

The following categories of extent of disease at baseline will also be summarized: number of patients with bone marrow aspirate, bone marrow aspirate results (% plasma cells, %Kappa/Lambda ratio performed, Kappa/Lambda ratio), number of patients with bone marrow aspirate/biopsy, bone marrow aspirate/biopsy results (% plasma cells, % cellularity, type of cellularity, Kappa/Lambda ratio), number and percentage of lytic bone lesions presenting in imaging, and number and percentage of extramedullary plasmacytoma present in imaging

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 summarized separately

Percentages for all categorical summarizations for bone marrow biopsy and aspirate is based on patients with an adequate sample for the specified test.

7.5 Medical History and Concurrent Medical Conditions

General medical history will be summarized (as frequency and percentage), using the safety population by Medical Dictionary for Regulatory Activities (MedDRA) system organ class, high level term, and preferred term. A patient is counted only once within each MedDRA. Percentages are based on the number of patients in the safety population.

General medical history will be listed for all patients.

7.6 Medication History and Concomitant Medications

Prior and concomitant medications will be listed for all patients in the safety population.

Concomitant medications will be summarized (as frequency and percentage) by World Health Organization Drug (WHODrug) Dictionary anatomical main group and preferred term. A patient is counted only once within each WHODrug category. Percentages are based on the number of patients in the safety population.

7.7 Study Drug Exposure and Compliance

Eligible patients will take ixazomib in combination with daratumumab and dexamethasone at the following dose levels and schedules:

- ixazomib 4 mg oral on Days 1, 8, and 15 of each 28-day cycle
- daratumumab 16 mg/kg on Days 1, 8, 15 and 22 in cycles 1 and 2; on Days 1 and 15 in cycles 3 to 6; on Day 1 in cycles 7 and beyond
- dexamethasone 20 mg on Days 1, 2, 8, 9, 15, 16, 22 and 23 of each 28-day cycle

Patients will be treated with IDd until progression of disease or unacceptable toxicity leading to a discontinuation of treatment or study termination. At that time, an EOT assessment will be completed and patients will then enter the follow-up phase of the study.

Overall exposure to the treatment regimen and exposure to each study drug will be summarized. Summaries will be for the overall IDd regimen and by each study drug, and will include the number of treatment cycles, total amount of drug taken (in mg), total number of doses taken, extent of exposure, number and percentage of patients by treatment

cycle, and drug compliance. An aggregate summary of the numbers and percentages of patients who had cycles 1-6, 7-13, 14-20 and >20 will also be presented.

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.

Extent of Exposure (days) is calculated as (Last Dose Date of study drug – First Dose Date of study drug + 1).

Drug compliance is presented by relative dose intensity (RDI) and calculated as follows:

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

RDI will also be displayed as <50%, >=50% - < 80%, >=80% - < 100%, = 100% and > 100%.

The actions on each study drug (dose reduction, held, missed, increased, delayed, discontinued permanently, etc) will be summarized for all patients., and by each cycle, aggregated for Cycles 1-6, 7-12, 13-20 and >20 if there is sufficient data for analysis.

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

7.8 Efficacy Analysis

Response will be assessed according to the International Myeloma Working Group (IMWG) criteria (in protocol appendix section) for all patients at every cycle during the treatment period and subsequently every 4 weeks during the PFS follow-up period until disease progression or patient is off the study. A response assessment (sCR, CR, VGPR, PR, SD) is considered confirmed if the next evaluable response assessment is the same or better. A response assessment of PD is considered confirmed if the next assessment is PD. In case there is only one PD as the last assessment, this PD is considered confirmed if either the EOT reason is PD or alternate therapy immediately follows the last assessment.

7.8.1 Primary Efficacy Endpoint

The primary endpoint is the combined best confirmed response rate of CR + VGPR. The primary efficacy analysis will be based on the response-evaluable population.

Estimates of combined best confirmed response of CR + VGPR rates will be presented with 2-sided 95% exact binomial confidence intervals.

Additionally, the best response rate will be summarized by cycle. Best response rates at the end of a cycle are based on the number of subjects treated for at least that many cycles. Best response at the end of a cycle is the best response (confirmed or unconfirmed) at or before the cycle for subjects who have been treated for at least that many cycles."

7.8.2 Secondary Efficacy Endpoints

The secondary efficacy parameters include PFS, TTP, OS, ORR, TTR and DOR.

Progression Free Survival

PFS is defined as the time from the date of the first administration of any study drug treatment to the date of the first documentation of disease progression based on the investigator's assessment or death due to any cause, whichever occurs first. Patients without documentation of PD or death will be censored at the date of last response assessment that is SD or better.

Time to Progression

TTP is defined as the time from the date of the first administration of any study drug treatment to the date of the first documentation of disease progression based on the investigator's assessment. Patients without documentation of PD will be censored at the date of last response assessment that is SD or better.

Overall Survival

OS is defined as the time from the date of first dose of any study drug treatment to death due to any cause. A patient without documentation of death at the time of analysis will be censored at the last visit at which s/he was known to be alive.

Overall Response Rate

ORR is defined as the rate of patients with response of CR + VGPR + PR before PD or subsequent therapy and will be analyzed in the response evaluable population.

Time to Response

TTR is defined as the time from the date of first dose of any study drug treatment to the date of first documented PR or better and will be analyzed in the response evaluable population.

Duration of Response

DOR is defined as the time from the first documentation of PR or better to the date of first documented progression among those patients that responded. Responders without

documentation of PD will be censored at the date of last response assessment that is SD or better prior to the start of alternative therapy. DOR will be analyzed in the response evaluable population of patients with a confirmed response of PR or better.

PFS, TTP and OS will be analyzed in the safety population. Kaplan-Meier (KM) analysis will be used to estimate PFS, TTP and OS if applicable. The quartiles (if estimable) and median follow-up, along with their 2-sided 95% CIs, will be provided. For patients who were censored, the reason for censoring will be summarized. The KM survival curves will also be produced.

The details regarding the handling of missing assessments and censoring for the PFS analysis are presented in the table below.

Table 7-1 Handling of Missing Assessments and Censoring for PFS Analysis Based on FDA guidance

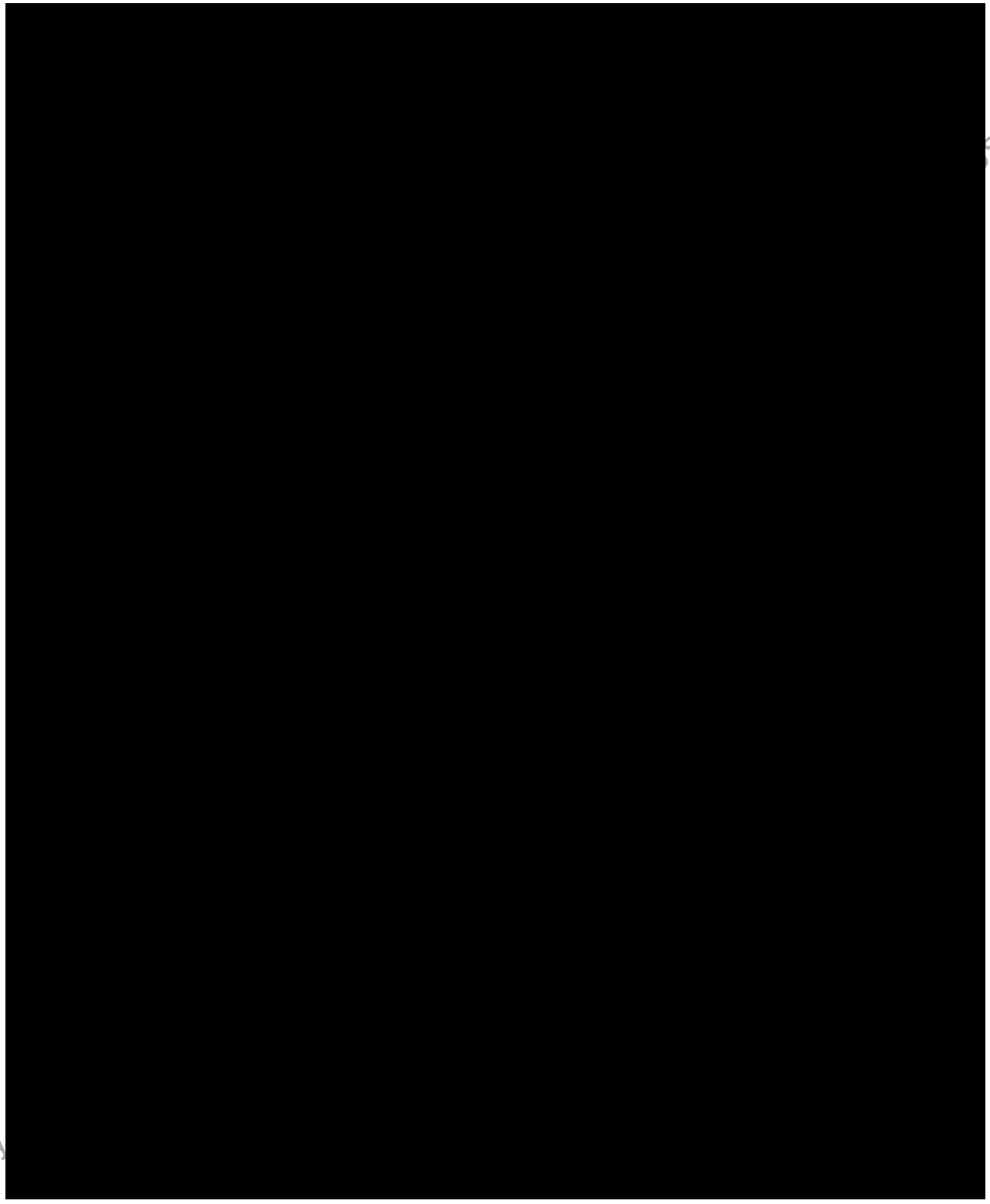
Situation	Date of Progression or Censoring	Outcome
No baseline and/or no post baseline assessment, no subsequent anticancer therapy after study treatment, no death	Date of Randomization	Censored
Disease progression documented between scheduled visits	Date of next scheduled visit	Progressed
No documented death or disease progression	Date of last adequate assessment[a]	Censored
Lost to follow-up, withdraw consent before any documented death or disease progression	Date of last adequate assessment[a]	Censored
Death or progression after more than 1 missed visit[b]	Date of last adequate assessment[a]	Censored
Alternate antineoplastic therapy started prior to disease progression	Date of last adequate assessment prior to starting alternate antineoplastic therapy	Censored
Death before first assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed

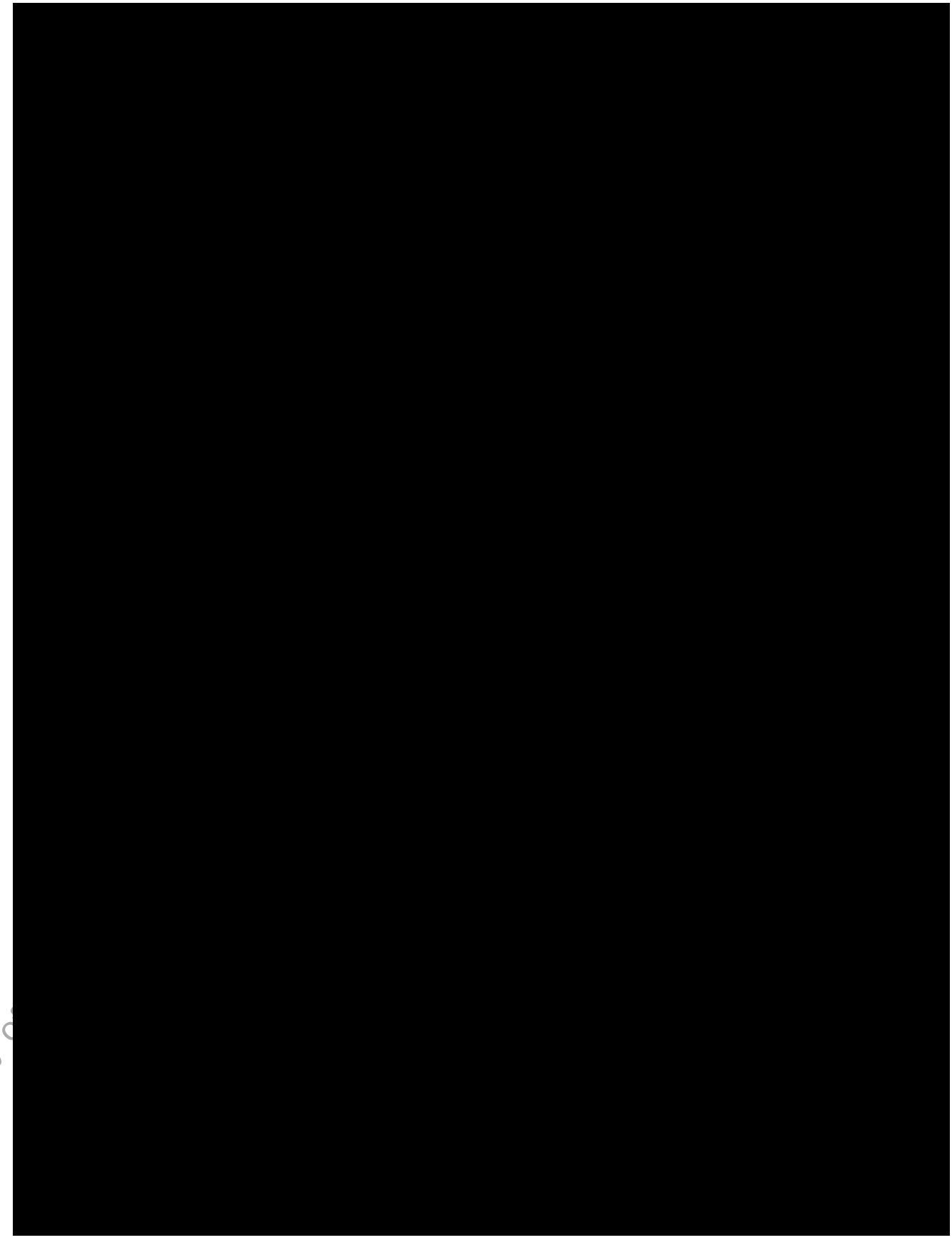
a Adequate disease assessment is defined as there being sufficient data to evaluate a patient's disease status.

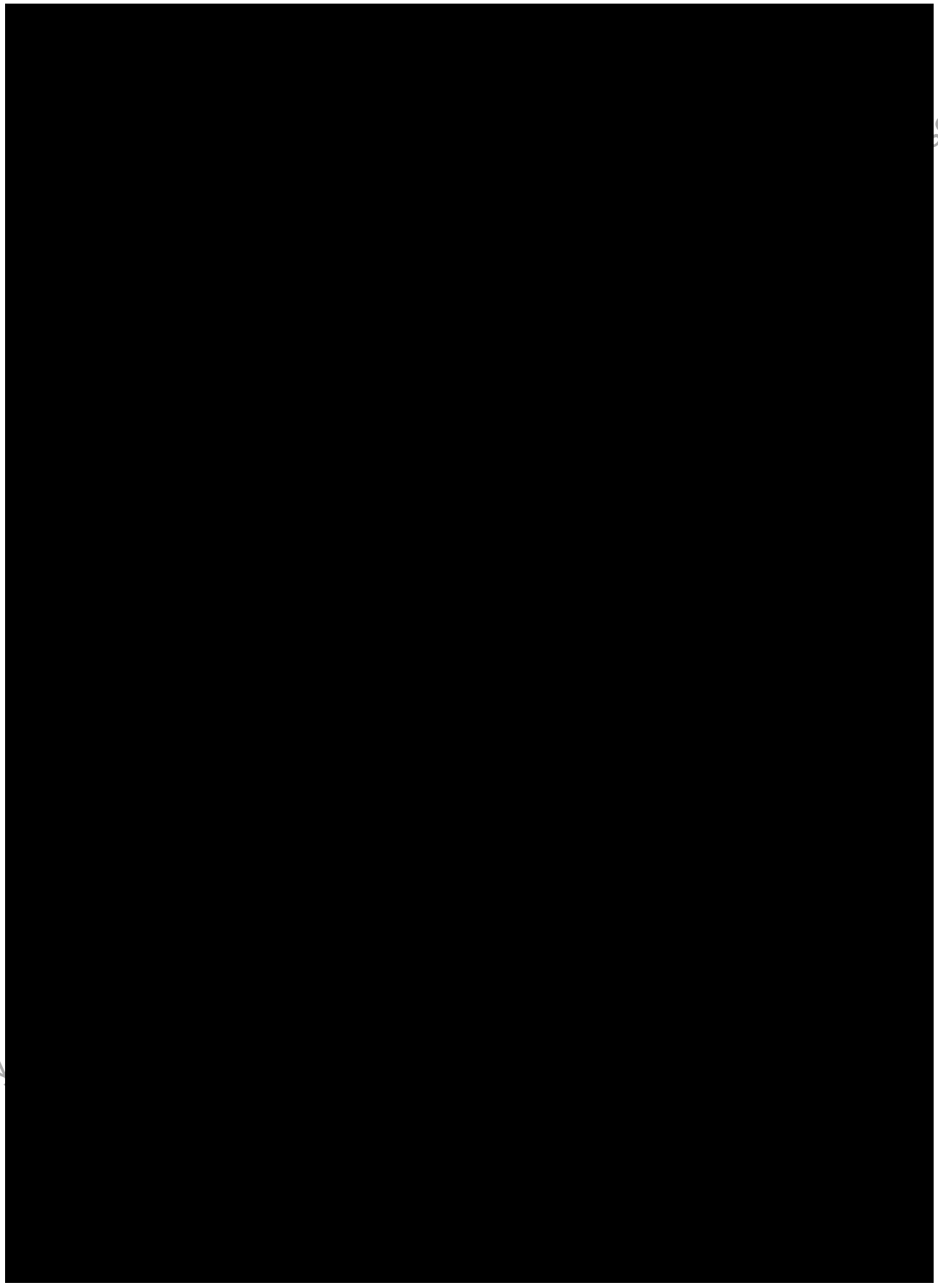
b Death or progression occurs more than 90 days from the previous adequate assessment.

7.8.3 Additional Efficacy Endpoint(s)

[redacted]







[redacted]

7.9 Pharmacokinetic Analysis

The ixazomib plasma concentration-time data will be listed and summarized by time point using descriptive statistics. PK data collected in this study will contribute to future population PK analyses of ixazomib. These analyses may include data from other ixazomib clinical studies. The analysis plan for the population PK analysis will be defined separately and the results will be reported separately. The PK data collected in this study may also contribute to exposure-response analyses. The results of any exposure-response analyses will be reported separately.

7.10 Safety Analysis

Safety will be evaluated by the incidence, intensity, types of adverse events (AEs), clinically significant changes in the patient's vital signs, weight, and clinical laboratory results in the safety population.

7.10.1 Adverse Events

7.10.1.1 Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0 or higher. All AEs will be presented in a by-patient listing.

Treatment-emergent AEs are AEs that occur after administration of the first dose of any study drug and through 30 days after the last dose of any study drug.

AEs will be tabulated according to MedDRA by system organ class, high level terms and preferred terms and will include the following categories:

- TEAEs
- Drug-related TEAEs

- Grade 3 TEAEs
- Grade 3 drug-related TEAEs
- Grade 4 or higher TEAEs
- Grade 4 or higher drug-related TEAEs
- The most commonly reported TEAEs (ie, those reported by ≥10% of all patients)
- All SAEs
- New primary malignancies
- Any AE resulting in dose modification or discontinuation of any study therapy.
- Any other AEs that in the opinion of the investigator is a clinically significant event.

Patients reporting 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 for Adverse Events (NCI CTCAE) using the most current published version. Patients reporting the same AE more than once will have the maximum intensity of that event counted within each body system, once within each high level term, and once within each preferred term.

The most commonly reported treatment-emergent AEs (ie, those events reported by ≥10% of all patients) will be tabulated by preferred term. Patients reporting the same AE more than once will have that event counted only once within each preferred term.

AECI table (TEAE of Clinical Importance) will also be tabulated by System Organ Class and Preferred Term

An overall summary AE table will include numbers and percentages of patients who had any AE, drug-related AE, Grade 3 AE, Grade 3 or higher AE, Grade 3 drug-related AE, Grade 3 or higher drug-related AE, Grade 4 or higher AE, Grade 4 or higher drug related AE,serious adverse event (SAE), drug-related SAE, AE resulting in study drug modification/discontinuation/reduction, and on-study deaths. An on-study death is defined as a death that occurs between the first dose of any study drug and within 30 days of the last dose of any study drug.

A by-patient listing of treatment-emergent AEs resulting in discontinuation of study drug regimen will be presented.

7.10.1.2 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 SAE will be summarized similarly.

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

7.10.1.3 Deaths

A by-patient listing of deaths will be presented. All deaths occurring on-study and during follow-up will be displayed (regardless of treatment-emergent AE status).

7.10.1.4 Adverse Events Resulting in Discontinuation of Study Drug

A by-subject listing of TEAEs resulting in discontinuation of any study drug or any dose modification will be presented.

7.10.2 Clinical Laboratory Evaluations

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 laboratory will only be used when no central laboratory test results exist at the same scheduled sample collection time point.

If a patient has repeated laboratory values for a given time point, the value from the last evaluation will be used. The test closest to the first dose will be considered baseline.

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 are as follows:

- Hematology: hemoglobin, neutrophils (ANC), lymphocytes, monocytes, eosinophils and basophils, platelets, WBC
- Serum chemistry: albumin, alkaline phosphatase, AST, ALT, blood urea nitrogen (BUN), beta-microglobin, total bilirubin, creatinine, , uric acid,
- LDH, glucose, calcium, sodium, potassium, magnesium, phosphate, CO_2, and chloride.

Mean laboratory values over time will be plotted for the above laboratory parameters

Shift tables will be constructed for laboratory parameters to tabulate changes in NCI CTCAE for toxicity from baseline to post baseline worst CTC grade. the most current published CTCAE version will be used, Parameters to be tabulated will include:

- Hematology: hemoglobin, platelets, WBC, ANC, Lymphocyte, leukocyte
- Serum chemistry: ALT, AST, alkaline phosphatase, creatinine, total bilirubin, calcium, magnesium, potassium, sodium, and phosphate,blood urea nitrogen (BUN), albumin

Scatter plots of baseline versus worst postbaseline values for the above parameters will be generated.

By-patient listings to be presented include hematology, serum chemistry. Unscheduled laboratory test results will be listed and included in laboratory shift tables.

7.10.3 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. Change from Baseline will also be presented.

A by-patient listing will be presented.

7.10.4 12-Lead ECGs

Descriptive statistics for the actual values and changes from baseline in ECGs (PR Interval, QRS interval, QT interval, and Ventricular Rate) will be tabulated by time point.

ECG abnormalities will be presented in a data listing.

7.10.5 Other Observations Related to Safety

Eastern Cooperative Oncology Group (ECOG) performance status and change from Baseline will be summarized. Shifts from Baseline to the worst post-Baseline score will be tabulated by treatment arm.

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

Additional safety analyses may be performed to further define the safety profile of ixazomib and daratumumab.

7.11 Interim Analysis

An interim safety review will be conducted after the first 15 patients have been enrolled and have had the chance to have been treated for 4 cycles. First interim analysis will be

conducted 6 months after last patient is enrolled. Second interim analysis will be conducted after 50% of PFS events have occurred.

No formal statistical analysis is planned for the safety review. A DSMB is not indicated at this time for the study. However, the decision to convene a DSMB could be made an any time during the conduct of the study. A steering committee is planned and will review the safety data, a recommendation may be provided by the steering committee regarding the trial conduct.

7.12 Clinical Study Report

The first interim analysis on the best confirmed response rate of CR+VGPR will be conducted 6 months after the last patient is enrolled. At that time, all relevant data will be queried and cleaned; a database snapshot will be taken. If the study is claimed successful, CSR would be written prior to study completion.

Second interim analysis will be performed after 50% patients have experienced progression/death events. The safety analysis may be updated based on the available data. An addendum to the CSR may be written if warranted based on these analyses.

Final analysis will be conducted 1 year after 50% of the PFS events have occurred, and a CSR will be written following this analysis if not done so earlier.

7.13 Changes in the Statistical Analysis Plan

This is statistical analysis plan amendment 1 which clarifies that there are 2 interim analyses and one final analysis. There are no major change in statistical analysis method.

8.0 REFERENCES

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Pharmacovigilance Approval	17-Nov-2020 19:58 UTC
	Biostatistics Approval	17-Nov-2020 20:41 UTC
	Clinical Pharmacology Approval	17-Nov-2020 20:45 UTC
	Clinical Science Approval	17-Nov-2020 20:55 UTC
	Biostatistics Approval	18-Nov-2020 15:50 UTC