CLINICAL STUDY PROTOCOL

MDACC 2014-0379

Phase II Study of ixazomib as maintenance therapy for patients with AML and high risk MDS in remission

Indication: Maintenance therapy
Phase: Phase II

Protocol History
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Investigator and Study Center:

PI: Courtney DiNardo, MD,

MSCE
Co-PI: Jorge Cortes, MD
MD Anderson Cancer Center 1515 Holcombe Blvd
Unit 0428
713-794-1141

This is an investigator-initiated study. Courtney DiNardo, MD is the principle investigator and MD Anderson (MDACC) the study sponsor.

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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Common abbreviations used in oncology protocols are provided below. Program-specific or protocol-specific abbreviations must be added to this list, and unnecessary abbreviations removed, as applicable. Abbreviations that are retained should not be changed.

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
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
$AUC_{24\ hr}$	area under the plasma concentration versus time curve from zero to 24 hours

AUC_{inf}	area under the plasma concentration versus time curve from zero to infinity
AUC_{τ}	area under the plasma concentration versus time curve from zero to next dose
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
CL	clearance, IV dosing
CL_P	plasma clearance
CL_{Total}	total clearance
C_{max}	single-dose maximum (peak) concentration
CNS	central nervous system

Abbreviation	Term
CO_2	carbon dioxide
CR	complete remission
CRM	continual reassessment method
CRP	C-reactive protein
CSF-1R	colony-stimulating factor 1 receptor
CT	computed tomography
C_{trough}	single-dose end of dosing interval (trough) concentration
CV	cardiovascular
CYP	cytochrome P_{450}
DLT	dose-limiting toxicity
DME	drug metabolizing enzymes
DNA	deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
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
hERG	human ether-à-go-go related gene
HIV	human immunodeficiency virus
HNSTD	highest nonseverely toxic dose

Abbreviation	Term
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
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)
MedDRA	Medical Dictionary for Regulatory Activities
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
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
NPO	nothing by mouth
NYHA	New York Heart Association
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	Pharmacodynamics(s)
Pgp	P-glycoprotein
PK	pharmacokinetic(s)
PO	*per os*; by mouth (orally)
PR	partial remission ***or*** partial response *choose one*
PRO	patient-reported outcome
PSA	prostate-specific antigen
QD	*quaque die*; each day; once daily

Abbreviation	Term
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
SAE	serious adverse event
SC	Subcutaneous
SD	stable disease
SmPC	Summary of Product Characteristics
$t_{1/2}$	terminal disposition half-life
TGI	tumor growth inhibition
T_{max}	single-dose time to reach maximum (peak) concentration
UK	United Kingdom
ULN	upper limit of the normal range
US	United States
V_z	volume of distribution in the terminal phase
WBC	white blood cell
WHO	World Health Organization

1. BACKGROUND AND STUDY RATIONALE

1.1 Scientific Background

1.1.1 Disease Under Treatment

Effective therapies for relapsed AML and high-risk MDS represent an unmet clinical need. Standard intensive chemotherapy for AML consists of the nucleoside analogue cytarabine with or without an anthracycline as induction therapy, followed by consolidation therapy with repeated cycles of high-dose cytarabine and/or stem cell transplantation (SCT) once in a complete remission. With this therapy, CR rates are approximately 60-80%, however long-term cure rates are approximately 40% or less in younger adults.(1, 2) In older patients or those with poor-risk cytogenetics, CR rates are closer to 35-50% and cure rates with intensive front-line therapy are less than 10%, with a median survival of less than 9 months.(3, 4)

The median progression-free survival in adults with AML is less than 1 year and most patients with AML will still ultimately die of their disease.(5, 6) In patients with relapsed or refractory disease after front-line therapy, the prognosis is even more dismal, and there is a need to improve the results obtained with front-line therapy. Continued intensive chemotherapy may improve relapse free survival (RFS), but it is toxic and most patients are unable to receive continued intensive chemotherapy for an extended period of time.{Buchner, 1985 #6225} Newer agents with novel mechanisms of action that demonstrate single-agent activity in leukemia may be able to circumvent resistance mechanisms and improve clinical outcomes by reducing the relapse rate once remission is attained. Considering the high remission rate with standard chemotherapy, a potential way to employ such agents is to administer them to patients who have achieved and sustained a CR after front-line therapy in an attempt to eradicate any detectable or undetectable minimal residual disease (MRD) and to therefore improve RFS and OS.

Relative to normal hematopoietic cells, AML blasts and leukemic stem cells (LSCs) have higher levels of NFκB activity, contributing to pro-survival signaling and chemoresistance. Modulating NFκB activity with ixazomib may therefore represent an important therapeutic

approach that can target LSCs and modulate chemoresistance.

1.1.2 Ixazomib

1.2 Preclinical Experience

Please refer to the current ixazomib Investigator's Brochure (IB).

1.3 Clinical Experience

Ixazomib has been evaluated as an oral single agent in phase 1 studies that have included patients with advanced solid tumors, lymphoma, relapse/refractory MM (RRMM), and relapsed or refractory light-chain (AL) amyloidosis and demonstrated early signs of activity. Ongoing studies continue to investigate both single-agent ixazomib and ixazomib in combination with standard treatments. Based on encouraging preliminary data observed in patients with MM requiring systemic treatment, 2 phase 3 trials in newly diagnosed MM (NDMM) (C16014) and RRMM (C16010) patient populations are currently evaluating ixazomib in combination with Revlimid and Dexamethasone (RevDex) versus placebo/RevDex. Both trials are combining ixazomib at a weekly dose of 4.0 mg on Days 1, 8, and 15 in a 28-day cycle to a standard dose of lenalidomide with a weekly dexamethasone dose of 40 mg. In addition, ongoing clinical pharmacology studies include evaluation of drug-drug interactions with ketoconazole and rifampin, effect of food, and oral bioavailability. Studies evaluating the safety and pharmacokinetic (PK) of ixazomib alone (in Japanese patients) and in combination with lenalidomide and dexamethasone in Asian adult patients (including Japanese patients) with a diagnosis of NDMM are ongoing.

As of 27 March 2013, preliminary clinical data is available for a total of 653 patients across 13 studies. The emerging safety profile indicates that ixazomib is generally well tolerated. The adverse events (AEs) are consistent with the class-based effects of proteasome inhibition and are similar to what has been previously reported with VELCADE though the severity of some, for example peripheral neuropathy, is less. While some of these potential toxicities may be severe, they can be managed by clinical monitoring and standard medical intervention, or, as needed, dose modification or discontinuation.

Fatigue was the most common AE reported among 384 patients treated in the oral (PO) studies (47%). Other common AEs reported in the pooled intravenous (IV) and PO safety populations include nausea, thrombocytopenia, diarrhea, and vomiting. Rash is also a

commonly reported treatment-emergent event; however, there is some variety in its characterization and causality resulting in different preferred terms to describe it. A high-level term outline of rash events includes rashes, eruptions and exanthems NEC; pruritus NEC; erythemas; papulosquamous conditions; and exfoliative conditions. The dose escalation phases of most trials reported in the IB have now completed enrollment, and gastrointestinal (GI) symptoms were the common dose-limiting toxicities (DLTs) when the use of prophylactic anti-emetics was not permitted per protocol. In the expansion cohorts or phase 2 cohorts (as per each study), the incidence and severity of GI symptoms was mitigated by the use of the lower maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) (as per each study) and standard clinical usage of anti-emetics and/or antidiarrheal medications as deemed appropriate. Prophylactic use of anti-emetics has not been required as with other agents but (as outlined in Section 6.7) has been used according to standard practice and are effective.

The most frequent (at least 20%) treatment-emergent adverse events (TEAEs) reported with the PO formulation pooled from single-agent studies (n = 201) irrespective of causality to ixazomib, include nausea (53%), fatigue (51%), diarrhea (44%), thrombocytopenia (34%), vomiting (38%), decreased appetite (32%), fever (21%), and anemia (21%). The most frequent (at least 20%) TEAEs reported with the PO formulation pooled from combination trials (irrespective of the combination) (n = 173), irrespective of causality to ixazomib, include diarrhea (47%), fatigue (44%), nausea (38%), peripheral edema (35%), constipation (33%), insomnia (29%), thrombocytopenia (28%), anemia (26%), vomiting (26%), neutropenia (25%), back pain (24%), pyrexia (23%), peripheral edema (21%, each), fever (20%), cough (20%), hypokalemia (20%), neutropenia (20%), and upper respiratory tract infection (20%). Overall rash of all grades is reported in approximately 50% of patients and is more common when ixazomib is given in combination with lenalidomide where rash is an overlapping toxicity.

Additional detailed information regarding the clinical experience of ixazomib may be found in the IB, including information on the IV formulation.

1.4 Pharmacokinetics and Drug Metabolism

Clinical IV and PO PK data show that ixazomib citrate (measured as the biologically active boronic acid form of ixazomib [MLN2238]) has multi-exponential disposition with a rapid initial phase that is largely over by 4 hours. Oral ixazomib citrate is rapidly absorbed with a

median single-dose first time of occurrence of maximum (peak) concentration (T_{max}) of approximately 0.5 to 2.0 hours and a terminal disposition half-life ($t_{1/2}$) after multiple dosing of approximately 5 to 7 days [1]. Results of a population PK analysis (n = 137) show that there is no relationship between body surface area (BSA) or body weight and clearance (CL). Also, based on stochastic simulations for fixed dose, exposures are independent of the individual patient's BSA [2]. Based on these data, a recommendation was made for fixed dosing in clinical trials. An absolute bioavailability of 67% was determined for ixazomib using the population PK analysis. Please refer to the current ixazomib IB and Safety Management Attachment (SMA) for information on the PK for IV doses of ixazomib.

Metabolism appears to be the major route of elimination for ixazomib, and urinary excretion of the parent drug is negligible (< 5% of dose). In vitro studies indicate that ixazomib is metabolized by multiple cytochrome P450s (CYPs) and non-CYP enzymes/proteins. The rank order of relative biotransformation activity of the 5 major human CYP isozymes was 3A4 (34.2%) > 1A2 (30.7%) > 2D6 (14.7%) > 2C9 (12.1%) > 2C19 (< 1%). Ixazomib is not an inhibitor of CYPs 1A2, 2C9, 2C19, 2D6, or 3A4 nor a time-dependent inhibitor of CYP3A4/5. The potential for ixazomib treatment to produce drug-drug interactions (DDIs) via CYP inhibition is inferred to be low. However, there may be a potential for DDIs with a concomitant strong CYP3A4 or CYP1A2 inhibitor or inducer because of the potential for first-pass metabolism when ixazomib is administered via the PO route and because of the moderate contribution of CYP3A4- and CYP1A2-mediated metabolism of ixazomib in human liver microsomes. Ixazomib may be a weak substrate of P-glycoprotein (Pgp), breast cancer resistance protein (BCRP), and multidrug resistance associated protein (MRP2) efflux pump transporters. Ixazomib is not an inhibitor of Pgp, BCRP, and MRP2. The potential for DDIs with substrates or inhibitors of Pgp, BCRP, and MRP2 is, therefore, inferred to be low. Clinical Study C16009 (Arm 1) with ketoconazole, a strong CYP3A4 inhibitor, showed a 2-fold increase in area under the plasma concentration versus time curve (AUC) in the presence of ketoconazole. This resulted in the continued exclusion of strong CYP3A4 inhibitors in ongoing/planned clinical studies.

Further details on these studies are provided in the IB.

1.5 Clinical Trial Experience Using the Oral Formulation of ixazomib

As of 27 March 2013, a total of 507 patients with differing malignancies (multiple myeloma, AL amyloidosis, nonhematologic cancers, and lymphoma) have been treated in studies

evaluating the oral ixazomib formulation. These patients have been treated with different doses of ixazomib either as a single-agent treatment (in 201 patients) or in combination with currently clinically available treatments (in 306 patients). Information regarding the ongoing studies, patient populations, and doses investigated is included in Table 1-1.

Table 1-1 Clinical Studies of Oral Ixazomib

Trial/ Population	Description	Doses Investigated
C16003 RRMM N = 60	PO, TW, single agent	0.24-2.23 mg/m^2 TW MTD: 2.0 mg/m^2 DLT: rash, thrombocytopenia Closed to enrollment
C16004 RRMM N = 60	PO, W, single agent	0.24-3.95 mg/m^2 W MTD: 2.97 mg/m^2 DLT: rash, nausea, vomiting, diarrhea Closed to enrollment
C16005 NDMM N = 65	PO, W, combination with LenDex 28-day cycle	1.68-3.95 mg/m^2 W MTD: 2.97 mg/m^2 DLT: nausea, vomiting, diarrhea, syncope RP2D[a]: 4.0 mg fixed (switched to fixed dosing in phase 2, equivalent to 2.23mg/m^2) Closed to enrollment
C16006 NDMM N = 20	PO, TW (Arm A- 42 day cycle) and W (Arm B- 28 day cycle), combination with Melphalan and Prednisone	Arm A[a]: 3-3.7-mg fixed dose TW DLT: rash, thrombocytopenia, subileus Arm B[a]: 3-5.5-mg fixed dose, W DLT: Esophageal ulcer nausea, vomiting, hematemesis, thrombocytopenia, ileus, neurogenic bladder MTD = 3.0 mg
C16007 RRAL N = 27	PO, W, single agent	4-5.5-mg fixed dose[a] W DLT: thrombocytopenia, diarrhea, dyspnea, acute rise in creatinine, cardiac arrest MTD: 4.0 mg W
C16008 NDMM N = 64	PO, TW, combination with LenDex 21-day cycle	3.0-3.7-mg fixed dose[a] W MTD: 3.0 mg Closed to enrollment
C16009 Solid tumors, Lymphomas N = 54	PO, W, single agent	5.5-mg fixed dose[a] W
C16010 RRMM N = 200	PO, W, with LenDex versus placebo-LenDex	4.0 mg W
C16011 RRAL N = 4	PO, W, with Dex versus physician's choice of a Dex-based regimen	4.0 mg W
C16013 RRMM N = 9	PO, W, with LenDex	4.0 mg W

Table 1-1 Clinical Studies of Oral Ixazomib

Trial/ Population	Description	Doses Investigated
C16014 Symptomatic MM N=701	PO, combination with LenDex	ixazomib 4.0 mg or matching placebo on Days 1, 8, and 15, plus Len 25 mg on Days 1-21 (10 mg if low creatinine clearance, with escalation to 15 mg if tolerated) and Dex 40 mg (or 20 mg if >75 years old) on Days 1, 8, 15, and 22
C16015 Symptomatic MM with normal renal function or severe renal impairment N=28	PO, combination with Dex	Part A: ixazomib 3.0 mg on Day 1 Part B: ixazomib 4.0 mg on Days 1, 8, and 15, plus Dex 40 mg (or 20 mg if >75 years old) on Days 1, 8, 15 and 22 of a 28-day cycle
C16017 RR follicular lymphoma N=58	PO, W	4.0, 5.3, and 7.0 mg, W Treatment at RP2D once determined.
C16018 Advanced solid tumors or hematologic malignancies with varying degrees of liver dysfunction N=45	Part A: PO, Day 1 of 15-day cycle Part B: PO, W	1.5 mg (severe hepatic impairment), 2.3 mg (moderate hepatic impairment), or 4.0 mg (normal hepatic function)
TB-MC010034 RRMM N = 10	PO, W	4.0 mg, W Single agent: 4.0 mg Combination with Rd

Abbreviations: RRAL = Relapsed and/or refractory Primary systemic light chain (AL) amyloidosis; BSA = body surface area; Dex=dexamethasone; DLT = dose-limiting toxicity; IV = intravenously; LenDex = lenalidomide plus dexamethasone; MTD = maximum tolerated dose; NDMM = newly diagnosed multiple myeloma; PO = orally; RR= relapsed and/or refractory; RRAL= relapsed and/or refractory systemic light chain amyloidosis RRMM = relapsed and/or refractory multiple myeloma; TBD = to be determined; TW = twice weekly; W = weekly; RP2D= recommended phase 2 dose.

Note that blinded data from pivotal Studies C16010 and C16011 are not included.

a Approximate BSA and fixed dosing equivalence: 3 mg~ equivalent to 1.68 mg/m^2 BSA dosing; 4.0 mg ~ equivalent to 2.23 mg/m^2 BSA dosing; and 5.5 mg~ equivalent to 2.97 mg/m^2 BSA dosing.

Overview of the Oral Formulation of ixazomib

The emerging safety profile indicates that ixazomib is generally well tolerated. The adverse events (AEs) are consistent with the class-based effects of proteasome inhibition and are similar to what has been previously reported with VELCADE though the severity of some, for example peripheral neuropathy, is less. While some of these potential toxicities may be severe, they can be managed by clinical monitoring and standard medical intervention, or, as needed, dose modification or discontinuation.

In the 4 ongoing studies (C16003, C16004, C16007, and C16009) investigating single-agent oral ixazomib in patients with differing malignancies (multiple myeloma, AL amyloidosis, nonhematologic cancers, and lymphoma), a total of 201 patients have been treated as of 27 March 2013. These patients have been treated with different doses of ixazomib as they are all phase 1 trials. An overview of the most frequent (at least 10%) AEs occurring in the pooled safety population from single-agent oral ixazomib Studies (C16003, C16004, C16007, and C16009) is shown in Table 1-2.

Table 1-2 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Single-Agent Studies

Primary System Organ Class Preferred Term	Oral Single Agent Total n = 201 n (%)
Subjects with at Least One Adverse Event	197 (98)
Gastrointestinal disorders	160 (80)
Nausea	106 (53)
Diarrhoea	88 (44)
Vomiting	77 (38)
Constipation	46 (23)
Abdominal pain	33 (16)
General disorders and administration site conditions	151 (75)
Fatigue	103 (51)
Pyrexia	51 (25)
Oedema peripheral	27 (13)
Asthenia	31 (15)
Nervous system disorders	92 (46)
Headache	29 (14)
Dizziness	26 (13)
Neuropathy peripheral	21 (10)
Metabolism and nutrition disorders	107 (53)
Decreased appetite	64 (32)

Table 1-2 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Single-Agent Studies

Primary System Organ Class Preferred Term	Oral Single Agent Total n = 201 n (%)
Dehydration	37 (18)
Blood and lymphatic system disorders	98 (49)
Thrombocytopenia	68 (34)
Anaemia	42 (21)
Neutropenia	29 (14)
Lymphopenia	20 (10)
Skin and subcutaneous tissue disorders	90 (45)
Rash macular[a]	23 (11)
Musculoskeletal and connective tissue disorders	93 (46)
Back pain	24 (12)
Arthralgia	28 (14)
Respiratory, thoracic and mediastinal disorders	78 (39)
Cough	28 (14)
Dyspnoea	30 (15)
Infections and infestations	89 (44)
Upper respiratory tract infection	31 (15)

Source: Ixazomib Investigator's Brochure Edition 7

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, version 15.0.

Subject Incidence: A subject counts once for each preferred term. Percentages use the number of treated subjects as the denominator.

a Note that rash maculopapular and rash macular represent the 2 most common terms used to describe rash.

As of 27 March 2013, there are 5 studies actively enrolling patients with multiple myeloma to investigate oral ixazomib in combination with standard combination regimens.
The most frequent (at least 10%) AEs occurring in the pooled safety population from Studies C16005, C16006, C16008, and C16013 are shown for all grades (Table 1-3). Note that in combination trials, related is defined as related to any study drug in the combination regimen.

Table 1-3 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Combination Studies

Primary System Organ Class Preferred Term	Total Oral Combo Agent (5/6/8/13) n = 173 n (%)
Subjects with at Least One Adverse Event	163 (94)
Gastrointestinal disorders	139 (80)
Nausea	65 (38)
Diarrhoea	81 (47)
Vomiting	51 (29)
Constipation	57 (33)
General disorders and administration site conditions	132 (76)
Fatigue	76 (44)
Pyrexia	39 (23)
Oedema peripheral	61 (35)
Asthenia	20 (12)
Nervous system disorders	115 (66)
Headache	28 (16)
Dizziness	34 (20)
Neuropathy peripheral	45 (26)
Metabolism and nutrition disorders	91 (53)
Decreased appetite	25 (14)
Hypokalaemia	34 (20)
Blood and lymphatic system disorders	88 (51)
Thrombocytopenia	49 (28)
Anaemia	45 (26)
Neutropenia	43 (25)
Lymphopenia	20 (12)
Skin and subcutaneous tissue disorders	102 (59)
Rash maculopapular[a]	29 (17)
Rash macular[a]	22 (13)
Musculoskeletal and connective tissue disorders	99 (57)
Back pain	42 (24)
Pain in extremity	31 (18)
Arthralgia	22 (13)
Respiratory, thoracic and mediastinal disorders	80 (46)
Cough	36 (21)
Dyspnoea	26 (15)

Table 1-3 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Combination Studies

Primary System Organ Class Preferred Term	Total Oral Combo Agent (5/6/8/13) n = 173 n (%)
Infections and infestations	92 (53)
Upper respiratory tract infection	35 (20)
Psychiatric disorders	73 (42)
Insomnia	50 (29)

Source: Ixazomib Investigator's Brochure Edition 7

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, version 15.0.

Subject Incidence: A subject counts once for each preferred term. Percentages use the number of treated subjects as the denominator.

Data from ongoing blinded pivotal trials (C16010) are not included.

a Note that rash maculopapular and rash macular represent the 2 most common terms used to describe rash..

The clinical experience with ixazomib also shows early signs of antitumor activity as evidenced by at least a 50% reduction in disease burden in some patients and prolonged disease stabilization in others across all ongoing trials. The antitumor activity has been seen with single-agent ixazomib, when combined with established therapies, and across the malignancies studied (advanced solid tumors [3], non-Hodgkin's disease, Hodgkin's disease [4], relapsed and/or refractory multiple myeloma [RRMM; 5; 6], relapsed or refractory systemic light chain amyloidosis [RRAL; 7], and newly diagnosed multiple myeloma [NDMM; 8; 9; 10]) to date.

Though additional data are needed to characterize the clinical benefit of this drug, the emerging data supports the ongoing development of ixazomib.

1.6 Relapsed and/or Refractory Multiple Myeloma

The early development of ixazomib in patients with RRMM involves 2 studies (C16003 and C16004) with similar objectives, but each investigated 1 of the 2 dosing schedules commonly used with the first-in-class proteasome inhibitor, VELCADE.

Study C16003 is an open-label, dose escalation, phase 1 study of ixazomib dosing on a twice-weekly schedule on Days 1, 4, 8, and 11 of a 21-day cycle in adult patients with RRMM.(11, 12) Study C16004 is an open-label, dose escalation, phase 1 study of ixazomib dosing on a weekly schedule on Days 1, 8, and 15 of a 28-day cycle in adults patients with

RRMM.(13, 14, 15) Both studies have now completed enrollment. The DLTs in Study C16003 were rash macular and thrombocytopenia and the DLTs in C16004 were nausea, diarrhea, vomiting, and erythema multiforme.

In the dose escalation component of both studies, patients had multiple myeloma that had relapsed following at least 2 lines of therapy that must have included bortezomib, thalidomide (or lenalidomide), and corticosteroids. In both studies, when the MTD was established, cohorts of patients representing the heterogeneous patient population currently seen in clinical practice were to be enrolled into 1 of 4 expansion cohorts, including a relapsed and refractory cohort, a carfilzomib cohort, a proteasome inhibitor-naïve cohort, and a VELCADE-relapsed cohort.

Final study results are currently being analyzed, but preliminary data suggest that ixazomib has anti-tumor activity in heavily pretreated MM patients, with durable responses/disease control, and is generally well tolerated. Please refer to the ixazomib IB and SMA for further information.

1.7 Newly Diagnosed Multiple Myeloma (NDMM)

Multiple research paths are being explored in patients with NDMM with a focus on evaluating ixazomib in combination with agents commonly used across treatment settings. The development of ixazomib in combination with lenalidomide with dexamethasone (LenDex) in patients with NDMM who are transplant eligible or ineligible involves 2 studies (C16005 and C16008) with similar study designs except for a few key differences, namely the schedules of ixazomib and dexamethasone. Ixazomib is also being evaluated in combination with melphalan and prednisone (MP) for patients who are not transplant eligible due to age or coexisting morbidity (in Study C16006).

All 3 studies are phase 1/2, with phase 1 focusing on safety and phase 2 on efficacy (and further characterization of safety). Please refer to the ixazomib IB and SMA for further information.

1.8 Clinical Trial Experience Using the Intravenous Formulation of Ixazomib

See the IB for descriptions of the 2 studies that investigated IV ixazomib in advanced solid tumors and advanced lymphoma (Studies C16001 and C16002, respectively).

1.9 Study Rationale

In adult AML and high-risk MDS patients that achieve remission, the median progression-free survival is less than 1 year, and most patients will still ultimately die of their disease. Additionally, the median age of AML and MDS of 65 to 70 years of age prevents curative stem cell transplantation procedures in the majority of our patients. Thus additional therapies are warranted at the time of remission to prevent a very high risk of relapse.

Relative to normal hematopoietic cells, AML blasts and leukemic stem cells (LSCs) have higher levels of NFkB activity, which can contribute to pro-survival signaling and chemoresistance. The novel, orally bioavailable, reversible and selective small molecule 20S proteasome inhibitor ixazomib has been shown to induce apoptosis in cancer cells with downregulation of survival proteins including NFkB, phospho-Rb, and Bcl-2. Thus, modulating NFkB activity with ixazomib may represent an important therapeutic approach that can target any residual LSCs at the time of remission.

1.10 Potential Risks and Benefits

Please refer to the current ixazomib IB and SMA.

The clinical benefit of ixazomib continues to be studied in a comprehensive and global development plan that involves studies sponsored by Millennium. Ixazomib appears to show early signs of anti-tumor activity as evidenced by at least 50% reduction in disease burden in some patients, including patients that have been heavily pretreated as well as those with newly diagnosed MM, and prolongs stabilization of the underlying disease in other patients across all ongoing trials. The preliminary findings are favorable when considering historical and currently available therapies for the patient populations evaluated. Though additional data are needed to characterize the clinical benefit of this drug, the emerging data supports expanded development of ixazomib for the treatment of patients with advanced malignancy.

This study will be conducted in compliance with the protocol, good clinical practice (GCP), applicable regulatory requirements, and International Conference on Harmonisation (ICH) guidelines.

2. STUDY OBJECTIVES

2.1 Primary Objectives

The primary objective of this study is to determine the efficacy of ixazomib in patients with acute myeloid leukemia (AML) and high-risk myelodysplastic syndrome (MDS) in complete remission (CR) or complete remission with incomplete count recovery (CRi) assessed by improvement on relapse-free survival (RFS).

2.2 Secondary Objectives

The secondary objectives of the study are to determine the efficacy of ixazomib at eradicating MRD (minimal residual disease) as assessed by multiparameter flow cytometry, as well as to determine the safety of ixazomib in this patient population.

2.3 Tertiary/Exploratory Objectives

The exploratory objectives of this study are:

1. To evaluate molecular or other genetic features of the patients hematologic malignancy that may be predictive of response
2. Correlative laboratory studies of subjects including gene expression profiling and other biomarkers to determine the *in vivo* mechanism of action and biological effects

3. STUDY ENDPOINTS

3.1 Primary Endpoints

The primary efficacy endpoint is relapse free survival (RFS), defined as the interval from the date of the achievement of CR/CRi to the date of first objective documentation of disease relapse or death from any cause. Subjects who are lost to follow-up without documented relapse, or are alive at last follow-up without documented relapse will be censored at the date of their last response assessment.

3.2 Secondary Endpoints

The secondary endpoint is to evaluate the efficacy of ixazomib at eradicating MRD as assessed by multiparameter flow cytometry in those patients who are MRD positive at the start of study.

The safety endpoint will assess overall incidence and severity of all adverse events events using Common Toxicity Criteria v 4.0. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) most current

version will be utilized for adverse event reporting.
(http://ctep.cancer.gov/reporting/ctc.html).

3.3 Tertiary/Exploratory Endpoints

The following exploratory endpoints and correlative laboratory studies will be examined to determine the *in vivo* mechanism of action and biological effects of treatment, as well as to detect whether certain molecular or other genetic patterns can predict response to ixazomib:

- Correlation of initial cytogenetic and mutational status (of 28 genes known to be affected in myelodysplastic syndromes and acute leukemias) performed through the bone marrow and molecular diagnostics laboratory of MD Anderson.

- Gene expression profiling and gene-specific DNA methylation may be performed. DNA methylation will be assessed using bisulfite PCR assays (i.e. COBRA or pyrosequencing analysis) and gene expression profiling by real-time PCR analysis.

- Additional exploratory subgroup analyses will be performed where an adequate number of subjects are available in each subgroup to allow for meaningful interpretation of results and these include: age group, sex, race, response (CR vs CRi at start), prior history of MDS (yes/no), cytogenetic category, induction therapy and consolidation therapy received, ECOG performance score.

4. STUDY DESIGN

4.1 Overview of Study Design

This is an open-label single arm Phase II study in subjects with AML or high-risk MDS in CR/CRi. Patients will receive single 4mg oral dose of ixazomib on days 1, 8 and 15 of each 28-day cycle. Treatment with ixazomib will be administered for 12 cycles for patients who remain in CR.

For patients with MRD positive CR/CRi at study start, treatment with ixazomib may continue for a total of 12 cycles after achievement of MRD negativity is observed.

Patients who are experiencing clinical benefit may be eligible to continue therapy after the allotted 12 cycles after discussion with the PI and the discussion documented in the patient's medical record.

Subjects will be assessed for outcome status (i.e. maintenance of CR/CRi) every 3 cycles or as clinically indicated. Adverse events, compliance and concomitant medications will be assessed continually throughout the study; specific information will be requested at each study visit.

Study cycles will be administered every 28 days $\pm$ 5 days or upon resolution of any clinically significant study drug related AE to grade 0-1, whichever occurs first.

Administration of subsequent cycles should be administered when neutrophils recover to $\geq$ 0.5 x 10^9/L and platelets to $\geq$ 50 x 10^9/L, or to baseline levels prior to the start of the last cycle of therapy.

Ixazomib will be self-administered primarily on an outpatient basis; but may be administered as an inpatient. Patient compliance will be documented using the MD Anderson (MDACC) Research Medication Diary and will be assessed at each study visit.

4.2 Number of Patients

This study is planned for 40 patients. All patients who receive at least one dose of the study drug will be included in the efficacy and safety analysis. Subjects who do not receive any dose of the study drug will be replaced.

4.3 Duration of Study

Treatment will continue until discontinuation due to relapse or disease progression, unacceptable toxicity, or completion of therapy. Completion of therapy includes 12 cycles of ixazomib. Note that in patients with MRD positive disease at study start, treatment may continue for 12 cycles after achievement of MRD negativity is observed. For patients experiencing clinical benefit, treatment may be continued beyond 12 cycles if in the best interest of the patient.

5. STUDY POPULATION

5.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Male or female patients 18 years of age or older.

2. Voluntary written consent must be given before performance of any study related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

3. Female patients who:

- Are postmenopausal for at least 1 year before the screening visit, OR
- Are surgically sterile, OR
- If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through 90 days after the last dose of study drug, OR
- Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

Male patients, even if surgically sterilized (ie, status post-vasectomy), must agree to one of the following:

- Agree to practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug, OR
- Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

4. Patients must have a history of *de novo* or therapy-related AML (defined by WHO classification of $\geq$20% bone marrow blasts) or high-risk MDS (defined by IPSS or IPSS-R)

5. Patients must be in a documented CR/CRi from either their front-line or first salvage therapy as evidenced by $\leq$5% bone marrow blasts and absence of extramedullary disease. (For patients with prior MDS who then transformed to AML, therapy received for MDS is not considered prior therapy for AML)

6. Patients should have received at least 2 cycles of induction therapy or 1 induction and 1 consolidation cycle, OR patient should be considered to have completed all planned chemotherapy, OR patient is considered to be unable, unfit or unwilling to receive additional chemotherapy.

7. Eastern Cooperative Oncology Group (ECOG) performance 0, 1, or 2.

8. Patients must meet the following clinical laboratory criteria:

- Absolute neutrophil count (ANC) ≥ 500/mm^3 and platelet count ≥ 50,000/mm^3. Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days before study enrollment.
- Total bilirubin ≤ 1.5 × the upper limit of the normal range (ULN).
- Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≤ 3 × ULN.
- Calculated creatinine clearance ≥ 30 mL/min

5.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Female patients who are lactating or have a positive serum or urine pregnancy test during the screening period.
2. Failure to have fully recovered (ie, ≤ Grade 1 toxicity) from the reversible effects of prior chemotherapy.
3. Major surgery within 14 days before enrollment.
4. Radiotherapy within 14 days before enrollment. If the involved field is small, 7 days will be considered a sufficient interval between treatment and administration of the ixazomib.
5. Known central nervous system involvement.
6. Infection requiring systemic antibiotic therapy or other serious infection within 14 days before study enrollment.
7. Evidence of current uncontrolled cardiovascular conditions, including sustained hypertension (SBP >150mmHg on two or more readings one week apart without normalization in between) , clinically significant uncontrolled cardiac arrhythmias, Class III-IV NYHA congestive heart failure, or unstable angina, or myocardial infarction within the past 6 months.
8. Systemic treatment within 7 days, or the half life of the treatment, whichever is longer, before the first dose of ixazomib, with strong inhibitors of CYP1A2

(fluvoxamine, enoxacin, ciprofloxacin), strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, posaconazole) or strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort.

9. Ongoing or active systemic infection, history of hepatitis B or C virus infection, or known human immunodeficiency virus (HIV) positive.

10. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.

11. Known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent.

12. Known GI disease or GI procedure that is expected to interfere with the oral absorption or tolerance of ixazomib including difficulty swallowing. As determined by investigator.

13. Diagnosed or treated for another malignancy within 2 years before study enrollment or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.

14. Patient has ≥ Grade 3 peripheral neuropathy, or Grade 2 with pain on clinical examination during the screening period.

15. Administration of other investigational agents for the treatment of AML/MDS within 21days (or 5 times the terminal half life of the investigational treatment whichever is longer) of the start of this trial and throughout the duration of this trial.

16. At the time of registration, stem cell transplantation is not planned within the next 3 months.

6. STUDY PROCEDURES

6.1 Screening

The following procedures are performed during screening. These procedures are to be performed within 4 weeks prior to study drug administration, except where otherwise indicated.

A signed and dated IEC/IRB approved informed consent form must be obtained before any study specific procedures are performed. Procedures that are part of routine care are not considered study specific procedures. All subjects will be screened for eligibility before enrollment. Once the subject has met all inclusion criteria, they may be enrolled onto the study.

Table 6.1: Procedures during Screening

Procedures	Specifics
Informed consent	
Full History and Physical Examination	History – present illness, prior surgeries, other medical illnesses, review of systems, allergies, prior therapy for cancer and concurrent meds; Physical exam – record weight, and note abnormalities in any major organ system (including but not limited to neurologic, head and neck, lymph nodes, cardiovascular, pulmonary, abdomen, extremities)
Concomitant Medications	Documentation of last use of other investigational agents for treatment of AML/MDS including terminal half-life of the agent
Vital signs (including temperature, pulse, and blood pressure)	
ECOG performance status	
Urine or serum pregnancy test (females of child-bearing potential only)	Within 7 days prior to first dose
Disease status (IPSS or R-IPSS classification for MDS and WHO disease classification for AML) Note: Bone marrow aspirate and/or biopsy within 4 weeks prior to first dose of drug in all patients. *Cytogenetics and immunohistochemistries performed as indicated.*	Staging with bone marrow aspiration and/or biopsy for disease assessment.
Serum chemistries (repeat if screening chemistries completed greater than 72 hours prior to the first dose)	Sodium, potassium, blood urea nitrogen, creatinine, glucose, AST and/or ALT, total bilirubin, alkaline phosphatase
CBC with differential (repeat if screening test completed greater than 72 hours prior to the first dose)	Differential may be omitted if WBC $\leq 0.5 \times 10^9$/L

6.2 Study Drug Administration

Study calendar

PROCEDURES	Pre-Study Screen°	Cycle 1 Day 1	Cycle 1 Day 8	Cycle 1 Day 15	Day 1 of Cycle 2 onwards (+/- 5 days)	End of Treatment (+/- 5 days)
Informed Consent	X					
Medical History	X					
Vital Signs (including temperature, pulse and blood pressure)	X	X	X	X	X	X

Physical Exam and Performance Status	X	X			X	X
Concomitant Medications	X	X			X	X
CBC with differential	X*	X	X[2]	X[2]	X[1,2]	X
Blood Chemistries	X*	X	X	X	X	X
Bone marrow aspiration and/or biopsy	X				X[3]	X
IPSS score &/or WHO disease classification	X					
Pregnancy Test (females of child-bearing potential only)	X†					
AE and SAE assessment	X	X	X	X	X	X

°Screening must be performed within 4 weeks prior to study drug initiation / study start unless otherwise indicated
*CBC with differential and blood chemistries (sodium, potassium, BUN, creatinine, glucose, AST and/or ALT, total bilirubin, alkaline phosphate) must be performed within 72 hours of Cycle 1 Day 1
†Within 7 days of Day 1 in females of child-bearing potential
[1]ANC must be $\geq$ 500/mm^3 and platelet count must be $\geq$ 50,000/mm^3, or have recovered to baseline hematologic values
[2]If platelet count $\leq$25,000/mm^3 or ANC $\leq$ 500/mm^3 on any ixazomib dosing day, CBC should be repeated twice weekly until counts have exceeded the prespecified values (as per Section 6.3.1)
[3]Bone marrow aspiration and/or biopsy required for study entry, and every 3 cycles for primary outcome unless required more frequently as clinically indicated.

Ixazomib will be self-administered primarily on an outpatient basis; but may be administered as an inpatient. 3 doses of ixazomib corresponding to the three treatment days (days 1, 8 and 15) will be dispensed for the first cycle. For subsequent cycles, up to 1 month of therapy (3 doses) may be dispensed.

On day 1 (+/- 5 days) of each cycle the following procedures will be performed and

documented: physical exam including vital signs and performance status, evaluation of concomitant medications, laboratory analysis including CBC and serum chemistries, and assessment of any side effects.

Subjects will be assessed for outcome status (i.e. maintenance of CR/CRi) every 3 cycles or as clinically indicated. Adverse events, compliance and concomitant medications will be assessed continually throughout the study; specific information will be requested at each study visit.
Patient compliance will be documented using the MD Anderson (MDACC) Research Medication Diary and will be assessed at each study visit.

Destruction of unused study drug will be in accordance with the institution's drug destruction policy.

Ixazomib Administration

All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). Patients should be monitored for toxicity, as necessary, and doses of ixazomib should be modified as needed to accommodate patient tolerance to treatment; this may include symptomatic treatment, dose interruptions, and adjustments of ixazomib dose (see Section 6.3).

Capsules of ixazomib will also be referred to as study drug. Study drug will be supplied by Millennium as capsules of 2.3, 3.0 and 4.0 mg ixazomib.

The prescribed administration of ixazomib doses in this study is 4mg ixazomib on days 1, 8 and 15 in a 28 day cycle.

Patients should be instructed to swallow ixazomib capsules whole, with water, and not to break, chew, or open the capsules. Study drug should be taken on an empty stomach (no food or drink) at least 1 hour before or 2 hours after a meal. Each capsule should be swallowed separately with a sip of water. A total of approximately 8 ounces (240 mL) of water should be taken with the capsules.

Missed doses can be taken as soon as the patient remembers if the next scheduled dose is 72 hours or more away. A double dose should not be taken to make up for a missed dose. If the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose.

Ixazomib Destruction

Investigational ixazomib (expired or end of study) should be destroyed on site according to the institution's standard operating procedure. Be sure to document removal and destruction on drug accountability logs.

6.3 Dose-Modification Guidelines

6.3.1 Recommended ixazomib Criteria for Beginning or Delaying a Subsequent Treatment Cycle & Dose Modifications for Treatment Associated Toxicity

Treatment with ixazomib will use a cycle length of 28 days. For a new cycle of treatment to begin, the patient must meet the following criteria:

- ANC must be $\geq 500/mm^3$ and platelet count must be $\geq 50{,}000/mm^3$, or have recovered to baseline hematologic values
- All other nonhematologic toxicity (except for alopecia) must have resolved to $\leq$ Grade 1 or to the patient's baseline condition

If the patient fails to meet the above-cited criteria for initiation of the next cycle of treatment, dosing should be delayed for 1 week. At the end of that time, the patient should be re-evaluated to determine whether the criteria have been met. If the patient continues to fail to meet the above-cited criteria, delay therapy and continue to re evaluate. The maximum delay before treatment should be discontinued will be 4 weeks or at the discretion of the Principal Investigator.

All decisions for dose adjustments will be made by the MD Anderson treating physician.

For dosing recommendations upon recovery, refer to Table 6-2 and Table 6-3. Dose adjustments different than those described below are acceptable after discussion with the PI, and will require documentation of the rationale for such action.

Table 6-1 MLN908 Dose Adjustments

Dose Level	Dose (mg)
Starting Dose	4.0 mg
-1	3.0 mg
-2	2.3 mg
-3	Discontinue

Dosage adjustments for hematologic toxicity are outlined in Table 6-2.

Table 6-2 ixazomib Dose Adjustments for Treatment Related Hematologic Toxicities

Criteria	Action
Within-Cycle Dose Modifications	
• If platelet count ≤ 25×10^9/L or ANC ≤ 0.50×10^9/L on a ixazomib dosing day (other than Day 1)	• ixazomib dose should be withheld. • Complete blood count (CBC) with differential should be repeated twice weekly until the ANC and/or platelet counts have exceeded the prespecified values (see Section 6.3.1) on at least 2 occasions. • Upon recovery, ixazomib may be reinitiated with 1 dose level reduction.
Dose Modifications for Subsequent Treatment Cycles	
• Delay of > 2 weeks in the start of a subsequent cycle due to lack of toxicity recovery as defined in Section 6.2ANC < 0.50×10^9/L, platelet count < 50×10^9/L, or other nonhematologic toxicities > Grade 1 or not to the patient's baseline condition	• Hold ixazomib until resolution as per criteria Section 6.3. • Upon recovery, reduce ixazomib 1 dose level. • The maximum delay before treatment should be discontinued will be 4 weeks or at the discretion of the PI.
Dose Modifications for Subsequent Treatment Cycles	
• All hematologic toxicities	• For hematologic toxicity that occurs during a cycle but recovers in time for the start of the next cycle,: o If dose was reduced within the cycle, start the next cycle at that same dose. o If due to toxicity timing, ie, after Day 15 dosing thus a dose reduction was not required at that point in the cycle, reduce ixazomib by 1 dose level at the start of that cycle. o Do not reduce the dose both within a cycle and at the start of the cycle for the same most severe toxicity.

Treatment modifications due to ixazomib -related AEs are outlined in Table 6-3.

Table 6-3 Ixazomib Treatment Modification (Delays, Reductions, and Discontinuations) Due to Treatment Related Adverse Events (Non-Hematologic Toxicities)

Adverse Event (Severity)	Action on Study Drug	Further Considerations
Peripheral Neuropathy:		
Grade 1	• No action	Grade 1 signs and symptoms: asymptomatic; without pain or loss of function; clinical or diagnostic observations only [14]
New or worsening Grade 1 peripheral neuropathy with pain or Grade 2	• May hold study drug until resolution to Grade ≤ 1 or baseline	Grade 2 signs and symptoms: Moderate symptoms; limiting instrumental activities of daily living (ADL) [14]
New or worsening Grade 2 peripheral neuropathy with pain or Grade 3	• Hold study drug until resolution to Grade ≤ 1 or baseline • Reduce study drug to next lower dose upon recovery	Grade 3 signs and symptoms: severe symptoms; limiting self-care ADL; assistive device indicated [14]
New or worsening Grade 4 peripheral neuropathy	• Discontinue study drug	
Grade 2 Rash	• Symptomatic recommendations as per section 6.7	The investigator and project clinician may discuss considerations for dose modifications and symptom management.
Grade 3 nonhematologic toxicity judged to be related to study drug If not recovered to ≤ Grade 1 or baseline within 4 weeks	• Hold study drug until resolution to Grade ≤ 1 or baseline • Reduce study drug to next lower dose upon return to ≤/= Grade 1 or baseline	Symptomatic recommendations noted in Section 6.7

Table 6-3 Ixazomib Treatment Modification (Delays, Reductions, and Discontinuations) Due to Treatment Related Adverse Events (Non-Hematologic Toxicities)

Adverse Event (Severity)	Action on Study Drug	Further Considerations
Subsequent recurrence Grade 3 that does not recover to ≤ Grade 1 or baseline within 4 weeks	• Hold study drug until resolution to Grade ≤ 1 or baseline • Reduce study drug to next lower dose	Monitor closely, take appropriate medical precautions, and provide appropriate symptomatic care
Grade 4 nonhematologic toxicities judged to be related to study drug	• Consider permanently discontinuing study drug	Exceptions are cases in which the investigator determines the patient is obtaining a clinical benefit

Once ixazomib is reduced for any toxicity, the dose may not be re-escalated.

6.4 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

Systemic treatment with any of the following metabolizing enzyme inhibitors is not permitted during this study. (A drug-drug interaction [DDI] with a strong inhibitor would increase ixazomib exposure and could lead to a higher probability of an AE.):.

- Strong inhibitors of CYP1A2: fluvoxamine, enoxacin, ciprofloxacin
- Strong inhibitors of CYP3A: clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, and posaconazole

Systemic treatment with any of the following metabolizing enzyme inducers should be avoided unless there is no appropriate alternative medication for the patient's use. A DDI with a strong inducer would decrease MLN2238 exposure. (Rationale: Unlike with inhibitors, if there were to be a DDI with an inducer, ixazomib exposure would be less; therefore, there would be a reduced chance of an AE. However, there may be less chance for an antitumor effect, but that is not an absolute reason to be taken off ixazomib):

- Strong CYP3A inducers: rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, and phenobarbital

The dietary supplements St John's wort and Ginkgo biloba are not permitted.

The following procedures are prohibited during the study:

- Any antineoplastic treatment with activity against AML or MDS except for drugs in this treatment regimen.
- Radiation therapy (note that, in general, the requirement for local radiation therapy indicates disease progression).
- Platelet transfusions to help patients meet treatment criteria are not allowed within 3 days prior to study drug administration on any dosing day.

6.5 Permitted Concomitant Medications and Procedures

The following medications and procedures are permitted during the study:

- Antiemetics, including 5-HT3 serotonin receptor antagonists, may be used at the discretion of the investigator.
- Loperamide or other antidiarrheal should be used for symptomatic diarrhea at discretion of the investigator. The dose and regimen will be according to institutional guidelines. IVF should be given to prevent volume depletion.
- Growth factors (eg, granulocyte colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF], recombinant erythropoietin) are permitted. Their use should follow published guidelines and/or institutional practice; however, alternative usage may be reviewed with the principal investigator . Erythropoietin will be allowed in this study. Their use should follow published guidelines and/or institutional practice.
- Patients should be transfused with red cells and platelets as clinically indicated and according to institutional guidelines.
- Antiviral therapy such as acyclovir may be administered if medically appropriate.
- Concomitant treatment with bisphosphonates will be permitted, as appropriate.
- Patients who experience worsening neuropathy from baseline may be observed for recovery, and have dose reductions/delays as indicated in the protocol, and any supportive therapy or intervention may be initiated as appropriate at the discretion of the investigator.

- Supportive measures consistent with optimal patient care may be given throughout the study.

6.6 Precautions and Restrictions

- Fluid deficit should be corrected before initiation of treatment and during treatment.
- Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided with impaired renal function given reported NSAID-induced renal failure in patients with decreased renal function.

Pregnancy

It is not known what effects ixazomib has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following criteria:

- Postmenopausal for at least 1 year before the screening visit, OR
- Surgically sterile, OR
- If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through 90 days after the last dose of study drug, AND
- Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)
- Two forms of barrier contraception: Females - Diaphragm plus spermicide Males- Condom plusspermicide

Male patients, even if surgically sterilized (ie, status postvasectomy), must agree to 1 of the following:

- Agree to practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug, OR
- Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)
- Two forms of barrier contraception: 1. Condom 2. Spermicide

6.7 Management of Clinical Events

Adverse drug reactions such as thrombocytopenia, diarrhea, fatigue, nausea, vomiting, and rash have been associated with ixazomib treatment. Management guidelines regarding these events are outlined below. Further details of management of ixazomib AEs are described in Section 6 of the ixazomib IB.

Prophylaxis Against Risk of Reactivation of Herpes Infection

Patients may be at an increased risk of infection including reactivation of herpes zoster and herpes simplex viruses. Antiviral therapy such as acyclovir, valacyclovir, or other antivirals may be initiated as clinically indicated. Other antivirals are also acceptable.

Nausea and/or Vomiting

Standard anti-emetics including 5-hydroxytryptamine 3 serotonin receptor antagonists are recommended for emesis if it occurs once treatment is initiated; prophylactic anti-emetics may also be considered at the physician's discretion. Dexamethasone should not be administered as an anti-emetic. Fluid deficit should be corrected before initiation of study drug and during treatment.

Diarrhea

Prophylactic antidiarrheals will not be used in this protocol. However, diarrhea should be managed according to clinical practice, including the administration of antidiarrheals once infectious causes are excluded. Fluid intake should be maintained to avoid dehydration. Fluid deficit should be corrected before initiation of treatment and during treatment.

Erythematous Rash With or Without Pruritus

As with bortezomib, rash with or without pruritus has been reported with ixazomib, primarily at the higher doses tested and when given with agents where rash is an overlapping toxicity. The rash may range from limited erythematous areas, macular and/or small papular

bumps that may or may not be pruritic over a few areas of the body, to a more generalized eruption that is predominately on the trunk or extremities. Rash has been most commonly characterized as maculopapular or macular. To date, when it does occur, rash is most commonly reported within the first 3 cycles of therapy. The rash is often transient, self-limiting, and is typically Grade 1 to 2 in severity.

Symptomatic measures such as antihistamines or corticosteroids (oral or topical) have been successfully used to manage rash and have been used prophylactically in subsequent cycles. The use of a topical, IV, or oral steroid (eg, prednisone $\leq$ 10 mg per day or equivalent) is permitted. Management of a Grade 3 rash may require intravenous antihistamines or corticosteroids. Administration of ixazomib (and/or other causative agent if given in combination) should be modified per protocol and re-initiated at a reduced level from where rash was noted (also, per protocol).

In line with clinical practice, dermatology consult and biopsy of Grade 3 or higher rash or any SAE involving rash is recommended. Prophylactic measures should also be considered if a patient has previously developed a rash (eg, using a thick, alcohol-free emollient cream on dry areas of the body or oral or topical antihistamines). A rare risk is Stevens-Johnson Syndrome, a severe and potentially life-threatening rash with skin peeling and mouth sores, which should be managed symptomatically according to standard medical practice. Punch biopsies for histopathological analysis are encouraged at the discretion of the investigator.

Thrombocytopenia

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Thrombocytopenia may be severe but has been manageable with platelet transfusions according to standard clinical practice. Ixazomib administration should be modified as noted as per dose modification recommendations in the protocol when thrombocytopenia occurs (see Table 6-2). Therapy can be reinitiated at a reduced level upon recovery of platelet counts. A rare risk is thrombotic thrombocytopenic purpura (TTP), a rare blood disorder where blood clots form in small blood vessels throughout the body characterized by thrombocytopenia, petechiae, fever, or possibly more serious signs and symptoms. TTP should be managed symptomatically according to standard medical practice.

Neutropenia

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Neutropenia may be severe but has

been manageable. Growth factor support is not required but may be considered according to standard clinical practice. Ixazomib administration should be modified as noted as per dose modification recommendations in the protocol when neutropenia occurs (see Table 6-2). Therapy can be reinitiated at a reduced level upon recovery of ANCs.

Fluid Deficit

Dehydration should be avoided since ixazomib may cause vomiting, diarrhea, and dehydration. Acute renal failure has been reported in patients treated with ixazomib, commonly in the setting of the previously noted gastrointestinal toxicities and dehydration.

Fluid deficit should be corrected before initiation of study drug and as needed during treatment to avoid dehydration.

Hypotension

Symptomatic hypotension and orthostatic hypotension with or without syncope have been reported with ixazomib. Blood pressure should be closely monitored while the patient is on study treatment and fluid deficit should be corrected as needed, especially in the setting of concomitant symptoms such as nausea, vomiting, diarrhea, or anorexia. Patients taking medications and/or diuretics to manage their blood pressure (for either hypo- or hypertension) should be managed according to standard clinical practice, including considerations for dose adjustments of their concomitant medications during the course of the trial. Fluid deficit should be corrected before initiation of study drug and as needed during treatment to avoid dehydration.

Posterior Reversible Encephalopathy Syndrome

One case of posterior reversible encephalopathy syndrome, which ultimately resolved, has been reported with ixazomib. This condition is characterized by headache, seizures and visual loss, as well as abrupt increase in blood pressure. Diagnosis may be confirmed by magnetic resonance imaging (MRI). If the syndrome is diagnosed or suspected, symptom-directed treatment should be maintained until the condition is reversed by control of hypertension or other instigating factors.

Transverse Myelitis

Transverse myelitis has also been reported with ixazomib. It is not known if ixazomib causes transverse myelitis; however, because it happened to a patient receiving ixazomib, the possibility that ixazomib may have contributed to transverse myelitis cannot be excluded.

6.8 Preparation, Reconstitution, and Dispensing

Ixazomib is an anticancer drug and as with other potentially toxic compounds caution should be exercised when handling ixazomib capsules.

6.9 Packaging and Labeling

The study drug ixazomib capsules will be provided by Millennium. The study drug will be labeled and handled as open-label material, and packaging labels will fulfill all requirements specified by governing regulations.

The capsules are individually packaged in cold form foil-foil blisters in a child-resistant carton. There are 3 capsules in each wallet/carton.

6.10 Storage, Handling, and Accountability

Upon receipt at the investigative site, ixazomib should remain in the blister and carton provided until use or until drug is dispensed. The container should be stored at the investigative site refrigerated (36°F to 46°F, 2°C to 8°C). Ensure that the drug is used before the retest expiry date provided by Millennium. Expiry extensions will be communicated accordingly with updated documentation to support the extended shelf life.

In countries where local regulations permit, ixazomib capsules dispensed to the patient for take-home dosing should remain in the blister packaging and refrigerated as noted above until the point of use. The investigative site is responsible for providing the medication to the patient in the correct daily dose configurations. Comprehensive instructions should be provided to the patient in order to ensure compliance with dosing procedures. Patients who are receiving take-home medication should be given only 1 cycle of medication at a time. Patients should be instructed to store the medication refrigerated (36°F to 46°F, 2°C to 8°C) for the duration of each cycle. Patients should be instructed to return their empty blister packs to the investigative site, rather than discarding them. Reconciliation will occur accordingly when the patient returns for their next cycle of take-home medication. Any extreme in temperature should be reported as an excursion and should be dealt with on a case-by-case basis.

Because ixazomib is an investigational agent, it should be handled with due care. Patients should be instructed not to chew, break, or open capsules. In case of contact with broken capsules, raising dust should be avoided during the clean-up operation. The product may be harmful by inhalation, ingestion, or skin absorption. Gloves and protective clothing should be worn during cleanup and return of broken capsules and powder to minimize skin contact.

The area should be ventilated and the site washed with soap and water after material pick-up is complete. The material should be disposed of as hazardous medical waste in compliance with federal, state, and local regulations.

In case of contact with the powder (eg, from a broken capsule), skin should be washed immediately with soap and copious amounts of water for at least 15 minutes. In case of contact with the eyes, copious amounts of water should be used to flush the eyes for at least 15 minutes. Medical personnel should be notified. Patients are to be instructed on proper storage, accountability, and administration of ixazomib, including that ixazomib is to be taken as intact capsules.

6.11 Study Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified sub-investigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

6.12 Termination of Treatment and/or Study Participation

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The investigator also has the right to withdraw patients from the study for any of the following reasons:

- Adverse event that in the opinion of the investigator makes continued administration of ixazomib undesirable or unsafe
- Protocol violation that makes continued participation undesirable or unsafe
- Lost to follow-up
- Clinically significant progressive disease
- Study terminated
- Other

At the time of withdrawal, all study procedures outlined for the End of Study visit should be completed. The primary reason for patient's withdrawal from the study should be recorded in the source documents and CRF.

6.13End of Study Visit:

Subjects will undergo an end of study visit at the time of discontinuation of ixazomib. Whenever possible, a laboratory analysis including CBC and serum chemistries along with a bone marrow aspirate and/or biopsy will be performed at this visit.

7. STATISTICAL AND QUANTITATIVE ANALYSES

7.1 Statistical Methods

This is a phase II study of ixazomib in AML/MDS patients who have achieved CR/CRi after front-line or first salvage therapy. Up to 40 patients will be enrolled in the study with an estimated accrual rate of one patient per month. The additional follow up will be 12 months after the last patient enrolls in the study. The primary objective is to evaluate relapse-free survival (RFS). The study will monitor futility and toxicity.

7.1.1 Determination of Sample Size and Futility Monitoring

Futility will be monitored for the study. We will monitor RFS using the methods of Thall et al. (2005), and we will stop enrolling patients to the study if we have reason to believe that the median RFS is less than that from the historical data, which is around 11 months. The trial will be stopped if Pr(lamda(E) > lamda(S) | data from the trial) < 0.05, where lamda(S) is the median RFS for standard treatment in the historical data with an inverse gamma distribution IG(123, 1342), which corresponds to a mean of 11 months and a standard deviation of 1 month, the corresponding 95%CI of (9.2, 13.1) months. The prior for lamda(E) is assumed to be IG(3.21, 24.31), corresponding to a mean of 11 months and a larger standard deviation of 10. Futility monitoring will start once 10 patients have been enrolled. Assuming an accrual rate of 1 per month and an additional follow-up of 12 months, the operating characteristics for the futility stopping rule under various true states are summarized in the following table 1, with results based on 5000 simulations.

Table 1: Operating characteristics for futility monitoring

Median OS (M)	Prob(Stop Early)	Mean No. of Patients (25%, 75%)
17	0.012	39.6 (40, 40)
14	0.036	39.1 (40, 40)
11	0.164	36.8 (40, 40)
8	0.673	28.2 (17, 40)

5	1	14.2 (10, 17)

Multc Lean V2.1 and OneArmTTE Version 4.1.1 were used for the trial design. The Department of Biostatistics will provide and maintain a website ("Clinical Trial Conduct": https://biostatistics.mdanderson.org/ClinicalTrialConduct/) for futility monitoring for each treatment arm on this study. The Clinical Trial Conduct website resides on a secure server, and access is gained through usernames and passwords provided to personnel responsible for enrolling patients and updating patient data. The website is accessed through a browser using secure socket layer (SSL) technology. Personnel responsible for enrolling patients on trials, which includes the principal investigator(s), research nurse(s), and data coordinator(s), will be trained by members of the Department of Biostatistics in the use of the trial website; the importance of timely updating of follow-up times and recording of events will be emphasized in training.

7.1.2 Populations for Analysis

All analyses including the efficacy and safety analysis will include all patients who have received at least 1 dose of study drug.

7.1.3 Demographic and Baseline Characteristics

Demographic and baseline laboratory results will be summarized using descriptive statistics, including means with standard deviations, or medians with ranges, histograms and box-plot. Fisher's exact test and Wilcoxon rank test will be used in the data analyses of categorical and continuous variables, respectively. Survival or times to failure and time to progression functions will be estimated using the Kaplan-Meier method. The two-sided log-rank test will be used to assess the differences of time to events between groups, and Cox proportional hazards model will also be fitted to evaluate the association between tiem-to-event outcomes with patient characteristics..

7.1.4 Efficacy Analysis

It is expected that the median RFS time will be 11 months or higher under this study treatment. If the trial continues to maximum accrual of 40 patients and maintains sufficient follow-up to observe 25 events (relapse/death) with a median RFS of 11 months, then a 95% credible interval for median RFS would extend from 7.4 to 16.3 months. The median RFS time will be estimated by Bayesian posterior estimates, along with the 95% credible intervals.

7.1.5 Safety Analysis

Unacceptable toxicities will also be monitored closely using the method of Thall et al (1995). Denote the probability of unacceptable toxicity by T_E, where toxicity is defined as any clinically significant treatment-related grade 3 or higher toxicities. We assume $T_E \sim$ beta (0.3, 0.7). We will stop the study if at any time point $Pr(T_E > 0.30 \mid data) > 0.9$. That is, we will stop the trial if, at any time during the study, we determine that there is more than 90% chance that the unacceptable toxicity rate is more than 30%. The trial will be stopped if (the number of severe toxicity observed / among number of patients)≥4/5, 6/10, 8/15, 9/20, 11/25, 13/30, 15/35. The toxicity stopping rules were created for examining data in patient cohorts of size 5.The operating characteristics are listed in table 2.

Toxicity will be reported by type, frequency and severity. Highest toxicity grades per patient per course will be tabulated for selected adverse events and laboratory measurements.

Table 2: OCs for unacceptable toxicity monitoring

True Prob(severe tox)	Pr(stop)	mean # Pts
0.1	0.0006	39.98
0.2	0.021	39.43
0.3	0.186	35.76
0.4	0.583	26.84
0.5	0.905	17.30

7.1.8. Study Endpoints

Relapse-Free Survival (RFS):
Is defined as the interval from the date of enrollment to the date of first objective documentation of disease relapse or death from any cause. Subjects who are lost to follow-up without documented relapse, or are alive at last follow-up without documented relapse will be censored at the date of their last response assessment.

Overall Survival (OS):
Time from date of treatment start until date of death due to any cause.

Complete Remission (CR):

Peripheral counts: No circulating blasts, neutrophil count $\geq$ 1 x 10^9/L and platelet count $\geq$ 100 x 10^9/L Bone marrow: $\leq$ 5% blasts, no detectable auer rods, no extramedullary leukemia with normal maturation of all cell lines. Persistent dysplasia will be noted.

Complete remission with incomplete count recovery (CRi):
Defined as a morphologic complete remission but the ANC may be <1 x 10^9/L or the platelet count may be <100 x 10^9/L.

Time to discontinuation from treatment will be assessed as an estimate of treatment failure/tolerability and is defined as the interval from the date of enrollment to the date of discontinuation. Subjects who are ongoing in treatment at the time of study closure will be censored at the date of last visit.

8. SAFETY AND ADVERSE EVENTS

8.1 Event Definitions

Adverse event reporting will be as per the NCI criteria and the MDACC Leukemia Specific Adverse Event Recording and Reporting Guidelines and the study will be monitored for compliance by the IND office

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) most current version (version 4.0) will be utilized for adverse event reporting. *(http://ctep.cancer.gov/reporting/ctc.html).*

Adverse drug reaction is a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function.

All "suspected adverse reactions" (as defined in 21 CFR 312.32(a)) will be captured in the case report forms. For abnormal chemical values grade 3 or 4, the apogee will be reported per course in the CRF.

Assessing causal connections between agents and disease is fundamental to the understanding of adverse drug reactions. In general, a drug may be considered a contributory cause of an adverse event if, had the drug not been administered, 1) the event would not have happened at all, 2) the event would have occurred later than it actually did, or 3) the event would have been less severe.

The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial. Protocol specific data and adverse events will be entered into PDMS/CORe, the electronic case report form for this protocol.

8.2 Serious Adverse Event Definition

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

Important medical events as defined above may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND office.

All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

Only unexpected AEs will be recorded in the Case Report Form (CRF). The Principal Investigator will sign and date the PDMS/CORe Case Report Form toxicity pages per each patient at the completion of each course. Following signature, the Case Report Form will be

used as source documentation for the adverse events for attribution.

All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

The following SAEs are not subject to expedited reporting, but would still be included in the annual report via the SAE log.

Disease progression leading to death, life-threating AE, hospitalization or prolongation of hospitalization, or disability

Reporting to FDA:

Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

8.3 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a female subject or partner of a male subject becomes pregnant during the study dosing period or within 3 months from the discontinuation of dosing, the investigator should report the information to the study supporter as if it is an SAE. The PI must immediately fax a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or

designee (see Section 8.3). The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated fertility date, pregnancy result and neonatal data etc., should be included in this information. The investigator will follow the medical status of the mother, as well as the fetus, as if the pregnancy is an SAE.

When the outcome of the pregnancy falls under the criteria for SAEs [spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly (including anomaly in a miscarried fetus)], the investigator should respond in accordance with the report procedure for SAEs. Additional information regarding the outcome of a pregnancy (which is categorized as an SAE) is mentioned below.

- "Spontaneous abortion" includes abortion and missed abortion.
- Death of an infant within 28 days after birth should be reported as an SAE regardless of its relationship with the study drug.
- Any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to MPI/PPD Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.
- In the case of a delivery of a living newborn, the "normality" of the infant is evaluated at the birth.
- "Normality" of the miscarried fetus is evaluated by visual examination unless test results which indicate a congenital anomaly are obtained prior to miscarriage.

8.4 SAE Reporting to Study Supporter (Millenium)

AEs may be spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. For serious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration. All SAEs, regardless of attribution, and adverse events related to study drug, will be entered in the CRF.

AEs which are serious must be reported to Millennium Pharmacovigilance (or designee) from the first dose of study drug through 30 days after administration of the last dost of ixazomib. Any SAE that occurs at any time after completion of ixazomib treatment or after the designated follow-up period that the principal investigator and/or sub-investigator considers to be related to any study drug must be reported to Millennium Pharmacovigilance (or designee). In addition, new primary malignancies that occur during the follow-up periods must be reported, regardless of seriousness or causality to study regimen, for a

minimum of three years after the last dose of the investigational product, starting from the first dose of study drug. All new cases of primary malignancy must be reported to Millennium Pharmacovigilance (or designee).

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned). All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

Since this is an investigator-initiated study, the principal investigator Dr. Courtney DiNardo, is responsible for reporting serious adverse events (SAEs) to any regulatory agency and to the investigator's EC or IRB.

Regardless of expectedness or causality, all SAEs must also be reported in English to Millennium Pharmacovigilance (or designee):

Fatal and Life Threatening SAEs within 24 hours of the principle investigator's observation or awareness of the event

All other serious (non-fatal/non life threatening) events within 4 calendar days of the principle investigator's observation or awareness of the event

See below for contact information for the reporting of SAEs to Millennium Pharmacovigilance.

The PI must fax or email the SAE Form per the timelines above. A sample of an SAE Form will be provided.

The SAE report must include at minimum:

- **Event term(s)**
- **Serious criteria**
- **Intensity of the event(s):** The PI or sub-investigator's determination. Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version specified in the protocol, as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.
- **Causality of the event(s):** PI's or sub-investigator's determination of the relationship of the event(s) to study drug administration.

Follow-up information on the SAE may be requested by Millennium.

Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version used at your institution, as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.

In the event that this is a multisite study, the PIis responsible to ensure that the SAE reports are sent to Millennium Pharmacovigilance (or designee) from all sites participating in the study. Sub-investigators must report all SAEs to the PI so that the PI can meet his/her foregoing reporting obligations to the required regulatory agencies and to Millennium Pharmacovigilance, unless otherwise agreed between the PI and sub-investigator(s).

Relationship to all study drugs for each SAE will be determined by the investigator or sub-investigator by responding yes or no to the question: Is there a reasonable possibility that the AE is associated with the study drug(s)?

The PI must also provide Millennium Pharmacovigilance with a copy of all communications with applicable regulatory authorities related to the study product(s), as soon as possible but no later than 4 calendar days of such communication.

SAE and Pregnancy Reporting Contact Information

SAE and Pregnancy Reporting Contact Information
Fax Number: 1-800-963-6290 Email: TakedaOncoCases@cognizant.com

Suggested Reporting Form:

- SAE Report Form
- US FDA MedWatch 3500A:

http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm

- Any other form deemed appropriate by the PI

9. ADMINISTRATIVE REQUIREMENTS

9.1 Product Complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact MedComm Solutions (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium Quality representative.

For Product Complaints, call MedComm Solutions at 877-674-3784 (877 MPI DRUG) (US and International)

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to Millennium Pharmacovigilance (refer to Section 8.3).

10. REFERENCES

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11. APPENDICES

11.1 Eastern Cooperative Oncology Group (ECOG) Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work)
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55.

12.COCKCROFT-GAULT EQUATION

For males:

$$\text{Creatinine Clearance} = \frac{(140\text{-age[years]} \times \text{weight [kg]})}{72 \times (\text{serum creatinine[mg/dL]})} \quad \text{OR} \quad \frac{(140\text{–age[years]} \times \text{weight [kg]})}{0.81 \times (\text{serum creatinine[µmol/L]})}$$

For females:

$$\text{Creatinine Clearance} = \frac{0.85\ (140\text{-age[years]} \times \text{weight [kg]})}{72 \times (\text{serum creatinine[mg/dL]})} \text{ OR } \frac{0.85\ (140\text{-age[years]} \times \text{weight [kg]})}{0.81 \times (\text{serum creatinine[µmol/L]})}$$

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.