CLINICAL STUDY PROTOCOL

X16013

UARK 2014-14: A Phase II Prospective Evaluation of Bone Remodeling During Ixazomib Treatment in Relapsed/Refractory Multiple Myeloma Patients

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Phase: 2

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This is an investigator-initiated study. The principal investigator is Maurizio Zangari, M.D. The University of Arkansas for Medical Sciences (UAMS) is the IND sponsor. The legal and ethical obligations of the principal investigator and the study sponsor are the joint obligations of Maurizio Zangari, M.D., and UAMS.

PROTOCOL SUMMARY

Study Title: Phase II prospective evaluation of bone remodeling during Ixazomib treatment in relapsed/refractory MM patients.

Phase: 2

Number of Patients: 20

Study Objectives

Primary

- To evaluate the effect of ixazomib on inducing osteoblast activation as measured by bone markers and imaging in patients with relapsed/refractory myeloma

Secondary

- To evaluate the association between osteoblastic activation and myeloma response to ixazomib
- To identify predictive factors for ixazomib-associated osteoblastic activation

Overview of Study Design:

Multiple myeloma (MM) is a clonal disease of plasma cells that is characterized by the accumulation of plasma cells in the bone marrow (and other organs) and sometimes results in bone marrow failure, bone destruction, hypercalcemia, and renal failure. It constitutes approximately 1% of all reported neoplasms and approximately 13% of hematologic cancers worldwide. Bone disease is extremely common at myeloma diagnosis. It is present in the majority of patients and is associated with bone pain, fractures, spinal cord compression, and hypercalcemia. Bone disease in myeloma results from the activation of osteoclast and suppression of osteoblast activity in the myelomatous bone marrow. As treatment and survival of myeloma patients improve, new therapies to reduce complications are important and vitally needed. The proteasome inhibitor, Bortezomib (VELCADE) has been shown to produce an anabolic bone effect (increase ALP, bone ALP, osteocalcin) in relapsed/refractory patients. This study will examine the bone anabolic effect in patients with relapsed/refractory myeloma with the next generation proteasome inhibitor, ixazomib, treatment (4mg day 1, 8, 15, 22 Q 28 days cycle x 6 cycles).

Study Population: Adult patients with confirmed diagnosis of relapsed/refractory multiple myeloma.

Duration of Study: 2 years

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LIST OF ABBREVIATIONS AND GLOSSARY 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
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
CO_2	carbon dioxide

Abbreviation	Term
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
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition

Abbreviation	Term
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IMWG	International Myeloma Working Group
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	progressive disease (disease progression) Progressive disease
Pgp	P-glycoprotein
PK	pharmacokinetic(s)
PO	*per os*; by mouth (orally)
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

Abbreviation	Term
QOD	*quaque altera die*; every other day
QOL	quality of life
QTc	rate-corrected QT interval (millisec) of electrocardiograph
RBC	red blood cell
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 RATIONALE

1.1. Scientific Background

1.1.1. Multiple Myeloma

Multiple myeloma (MM) is a clonal disease of plasma cells that is characterized by the accumulation of plasma cells in the bone marrow (and other organs) and sometimes results in bone marrow failure, bone destruction, hypercalcemia, and renal failure. It constitutes approximately 1% of all reported neoplasms and approximately 13% of hematologic cancers worldwide.(1) In the Americas, Canada, and Western European countries, approximately 5 to 7 new cases of MM are diagnosed per 100,000 people each year(1, 2, 3). Although less common in Asian countries, MM is a growing health problem with an incidence that is approaching western countries and a larger population base.(4, 5) In the United States, approximately 20,000 cases of MM are diagnosed each year and 10,650 deaths per year are due to the disease (approximately 2% of all cancer deaths).

MM is sensitive to many cytotoxic drugs including alkylating agents, anthracyclines, and corticosteroids for both initial treatment and relapsed disease. Over the past decade, significant achievements have been made in expanding treatment options for MM with novel therapies such as thalidomide, Bortezomib (VELCADE), and lenalidomide. These regimens have extended progression-free survival (PFS) and/or time-to-progression (TTP)(6, 7, 8, 9, 10). The introduction of novel therapies and the increased use of high-dose therapy significantly improved overall survival in patients with newly diagnosed myeloma who were eligible for autologous stem cell transplant (ASCT) (11, 12).

Despite the increase in the number of therapeutic options, the disease remains incurable and there is a need for new and better agents. Patients who relapse after their initial therapy demonstrate variable response to subsequent treatments with decreasing likelihood and duration of response (DOR). Patients ultimately become refractory to approved therapies and have no alternative treatment options. In an effort to further target the proteasome with improved activity in MM and other cancers, Millennium has developed ixazomib, a small molecule 20S proteasome inhibitor.

1.1.2. Bone Disease in Multiple Myeloma

Bone disease is extremely common at myeloma diagnosis (13). It is present in the majority of patients and is associated with bone pain, fractures, spinal cord compression, and hypercalcemia (14, 15). The pathogenesis of lytic bone disease in myeloma is complex and is associated with increased osteoclast activity through multiple interactions between myeloma cells and the bone marrow microenvironment, impairing osteoblast function which results in decreasing bone formation (13-15).

1.1.3. Bortezomib and MM Bone Disease

The proteasome inhibitor Bortezomib (VELCADE) has been shown through numerous clinical and preclinical studies to have an impact on bone health, density, and on the biomarkers related to osteoblast and osteoclast activity. Evidence indicates that Bortezomib demonstrates a bone anabolic effect as shown in Table 1 (16).

Table 1. Effects of bortezomib on bone health in myeloma: clinical data

Reference	Intervention	Clinical endpoints
Delforge et al. (analysis of VISTA study)	VMP: *n* = 344; MP: *n* = 338	Use of bisphosphonates: VMP = 73% of patients; MP = 82% Progression due to worsening bone disease: VMP = 3% of patients; MP = 11% Skeletal AEs (inc. pathologic fracture, spinal-cord compression, new osteolysis, vertebroplasty): VMP = 4% of patients; MP = 5%
Lee et al.	Bortezomib,*n* = 2	After three cycles of bortezomib treatment ^{99m}Tc-methyl-diphosphonate bone scans: increased uptake by osteoblasts was associated with re-building activity
Terpos et al.	Lenalidomide + dexamethasone ± bortezomib:*n* = 99	No skeletal-related events were observed in the bortezomib arm; two patients treated with lenalidomide/dexamethasone who had not responded to therapy developed a vertebral pathological fracture
Zangari et al.	Bortezomib:*n* = 16	A significant increase in bone volume/total volume from baseline (assessed via histomorphometric microCT) was observed in six of seven patients ($P < 0.02$) – In the responding patient, bone volume/total volume increased from 12% at baseline to 90% after 12 doses Change in median PTH in patients responding to bortezomib treatment was significant at days 11, 21 and 33 (all $P = 0.04$); mean PTH over dosing interval: 85.6 (SD: 16.9) No significant change was recorded in non-responders; mean PTH: 54.4 (SD: 7.1)
Berno et al.	Bortezomib:*n* = 16	Change in lumbar bone mineral density T-score of 0.36 (−0.76 at baseline) and at femoral neck bone density T-score of 0.25 (−1.31 at baseline), compared with baseline
Terpos et al.	Bortezomib + dexamethasone +zoledronic acid: *n* = 27	Significant ($P < 0.001$) increase in bone mineral density from baseline (mean [SD] T score: −2.59 ± 1.32) was reported after 8 weeks' therapy (−2.31 ± 1.30) in the lumbar spine (L1–L4, antero-posterior view), as assessed via dual energy X-ray absorptiometry; this was not echoed in the femoral neck Four patients showed at least a 10% increase in L1–L4 bone mineral density (median: 16%), all of whom responded to therapy (3 = PR, 1 = CR)
Terpos et al.	*Post ASCT*VDT:*n* = 42 (block 1*n* = 32; block 2*n* = 16)	Only one skeletal-related AE was observed
Ozaki et al.	Bortezomib + dexamethasone:*n* = 14	In two patients, a "dramatic improvement" in osteolytic lesions was observed (as assessed via multidetector CT scans)

AE, adverse event; ASCT, autologous stem-cell transplant; CR, complete response; CT, computed tomography; MP, melphalan–prednisone; PR, partial response; PTH, parathyroid hormone; VDT, bortezomib–dexamethasone–thalidomide; VISTA, Velcade as Initial Standard Therapy in Multiple Myeloma: Assessment with Melphalan and Prednisone; VMP, bortezomib–melphalan–prednisone.

Multiple studies of bortezomib in both treated and untreated myeloma patients have shown a positive effect of bortezomib on bone health, including fewer bone disease-related MM progression events, increases in bone volume, and improvements in osteolytic lesions. Alkaline phosphatase (total and bone isoenzyme), a marker of bone formation, is increased during bortezomib treatment; the degree of increase may be associated with treatment response. Bortezomib is also related to a reduction in Dickkopf-1, an inhibitor of osteoblast function. Increases of other bone-formation markers and decreases of bone-resorption markers, have also been seen. These clinical effects are supported by preclinical data suggesting bortezomib is associated with an increase in bone formation and osteoblast numbers/activity, arising from direct effects of bortezomib and proteasome inhibition. Thus, evidence indicates that bortezomib exerts a positive effect on bone metabolism in MM and has a bone anabolic effect (16).

1.1.4. Ixazomib (MLN9708)

1.1.4.1. Preclinical Experience

Please refer to the current ixazomib **Investigator's Brochure (IB) and Safety Management Attachment (SMA).**

1.1.4.2. Clinical Experience

Ixazomib has been evaluated as an oral single agent in phase 1 studies that have included patients with advanced solid tumors, lymphoma, relapsed/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 Investigator's Brochure,** including information on the IV formulation.

1.1.4.3. Pharmacokinetics and Drug Metabolism

Clinical IV and PO pharmacokinetic (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 is rapidly absorbed with a median time to first maximum plasma concentration (Tmax) of approximately 0.5 to 2.0 hours and terminal t1/2 after multiple dosing of approximately 5 to 7 days(14). 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 (15). 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**.

1.1.4.4. Clinical Trial Experience Using Oral Ixazomib

As of 27 March 2013, a total of 507 patients with differing malignancies (multiple myeloma, AL amyloidosis, non-hematologic 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 2.

Table 2 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

Table 2 Clinical Studies of Oral Ixazomib		
Trial/Population	**Description**	**Doses Investigated**
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
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 dysf 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

1.1.4.5. Overview of the Oral Formulation of Ixazomib

The emerging safety profile indicates that oral 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 3.

Table 3: 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)
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 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). In combination trials, related is defined as related to any study drug in the combination regimen.

Table 4 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)

Table 4 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 (%)
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)
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) (17), non-Hodgkin's disease, Hodgkin's disease (18), relapsed and/or refractory multiple myeloma [RRMM](19) relapsed or refractory systemic light chain amyloidosis [RRAL]; (20), and newly diagnosed multiple myeloma [NDMM]; (21-24) to date.

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

1.1.4.6. 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. (25) 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 (26, 27). 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.

1.1.4.7. 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.

1.1.4.8. Clinical Trial Experience Using IV 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).

1.1.4.9. Preclinical Activity of Oral Ixazomib in Myeloma Bone Disease

Ixazomib has demonstrated both preclinical and clinical activity. Gomez et al investigated its bone anabolic and antiresporptive effects in myeloma and in comparison with Bortezomib (VELCADE) in preclinical models. Clinically achievable concentrations of Ixazomib markedly inhibited osteoclast formation and resorption in ex vivo experiments, as well as promoted osteoblast differentiation and function (even in osteoprogenitor cells from MM patients with osteolytic lesions). In a mouse model, Ixazomib was found to be at least as effective as intraperitoneally administered Bortezomib in the control of myeloma growth and in the prevention of bone loss (28).

1.2. Study Rationale

Bortezomib has been shown to produce on anabolic bone effect in relapsed/refractory MM patients . The next generation proteasome inhibitor, Ixazomib, has been evaluated in a pre-clinical setting and has demonstrated to be as equally effective to Bortezomib in both controlling tumor burden and providing a significant benefit in associated bone disease (as sustained by both bone anabolic and anticatabolic activities (28).

Consequently, it is conceivable that this agent may achieve bone beneficial effects in addition to its anti-myeloma activity in multiple myeloma patients. Therefore, this study is designed to focus on the bone anabolic effect of Ixazomib (MLN 9708) on MM patients, with the primary objective of determining the effect of a short course of ixazomib (6 cycles) on changes in bone on formation markers (BALP,

osteocalcin) and bone densitometry (Dexascan) indicies. The dose of ixazomib will be given as 4mg weekly in a 28 day cycle for a maximum of 6 cycles.

1.3. Potential Risks and Benefits

Please refer to the current ixazomib Investigator's Brochure (IB) and Safety Management Attachment (SMA).

Risks of study drug:

Blood and lymphatic system disorders: Lymphopenia. Reductions in blood counts may predispose patients to an increased susceptibility to infection (see Infections and infestations below). A rare risk is thrombotic thrombocytopenic purpura, a rare blood disorder where blood clots form in small blood vessels throughout the body, characterized by thrombocytopenia, petechiae, fever, and possibly more serious signs and symptoms. Reticulocytopenia was described in animals and may be associated with anemia. These potential risks should be managed according to standard medical practice.

Gastrointestinal disorders: Intestinal obstruction including ileus and intussusception (described in animal studies), abdominal pain.

General disorders and administration site conditions: Chills, influenza like illness.

Infections and infestations: Pneumonia. Lymphopenia may be associated with increased risk of infection, including re-activation of herpes zoster. Antiviral therapy may be initiated as clinically indicated.

Investigations: Blood creatinine increased (see Renal and urinary disorders below).

Metabolism and nutrition disorders: Dehydration, electrolyte imbalance.

Musculoskeletal and connective tissue disorders: Back pain, myalgia, arthralgia, bone pain, pain in extremity.

Nervous system disorders: Headache, syncope. In addition, autonomic and motor neuropathy may be observed, as both have been reported for VELCADE, another proteasome inhibitor. Posterior reversible encephalopathy syndrome (PRES) has been reported with ixazomib. PRES has also been reported for VELCADE (refer to VELCADE for Injection Package Insert) and Kyprolis.(10) 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.

Renal and urinary disorders: Renal impairment, renal failures, and renal failure acute have been reported in association with dehydration due to nausea, vomiting, anorexia, and/or diarrhea, the use of nonsteroidal anti-inflammatory drugs (NSAIDs), and/or disease progression. In one situation, this has been severe, requiring temporary dialysis.

Respiratory, thoracic and mediastinal disorders: Dyspnoea, cough, upper respiratory tract infection, pneumonitis.

Skin and subcutaneous tissue disorders: A rare risk is Stevens-Johnson syndrome, a severe, life-threatening or deadly rash with skin peeling and mouth sores, which should be managed symptomatically according to standard medical practice. Stevens-Johnson syndrome has also been reported for VELCADE (refer to VELCADE for Injection Package Insert(10)). It is also reported as risk with lenalidomide, an agent used in the treatment of hematologic malignancies including in combination with proteasome inhibitors. For more information about this risk with lenalidomide, refer to the Revlimid (lenalidomide) Package Insert.(11)

Vascular disorders: Hypotension, orthostatic hypotension.

Other: Acute phase response that may result in fever and metabolic changes (observed only in

nonclinical studies). Infrequent incidences of tumor lysis syndrome have also been reported.

Potential Benefits:

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).

2. STUDY OBJECTIVES

2.1. Primary Objectives

To evaluate the effect of Ixazomib (MLN 9708) on inducing osteoblast activation as measured by change in serum osteocalcin from baseline to end of study in patients with relapsed/refractory multiple myeloma.

2.2. Secondary Objectives

To evaluate the effect of ixazomib on osteoblast activation as measured by change in radiological studies and bone marrow parameters from baseline to end of study.

To evaluate change from baseline in osteocalcin and other serum bone markers throughout ixazomib treatment.

To evaluate the association between osteoblastic activation and myeloma response to Ixazomib.

To identify predictive factors for Ixazomib-associated osteoblastic activation.

3. STUDY ENDPOINTS

3.1. Primary Endpoint

The primary endpoint of this study is change in serum osteocalcin from baseline to study exit.

3.2. Secondary Endpoint

The secondary endpoints of this study include change in serum osteocalcin and other serum bone markers (BALP, NTX, Vitamin D25) at each study visit, including the exit visit; change in bone marrow parameters (immunohistochemistry, cytogenetics, and flow cytometry) and Dexascan T scores from baseline to end of study; and association between bone marker and radiological changes and anti-myeloma activity in response to Ixazomib therapy.

4. STUDY DESIGN

4.1. Overview of Study Design

This is a phase 2 study designed to examine the bone anabolic effect of the next generation proteasome inhibitor, ixazomib, in relapsed/refractory myeloma patients. Treatment consists of ixazomib 4 mg on days 1, 8, 15, 22 of a 28-day cycle, for a maximum of 6 cycles).

General eligibility criteria may be assessed prior to the formal Screening period if it is part of standard clinical practice. However, per the Schedule of Events, formal screening will occur during the Screening period, which may last for up to 35 days prior to initiating study treatment. Determination of relapsed/refractory disease as an entry criterion may be based on patient data obtained during or following the patient's most recent prior antineoplastic therapy.

Study drug (ixazomib 4.0 mg) will be given on Days 1, 8, 15, 22 of a 28- day cycle for a maximum of 6 cycles. Dose modifications may be made based on toxicities during treatment. Patients will be discontinued from the study for progressive disease or unacceptable toxicity.

Treatment periods will be defined as 28-day cycles. Patients will be seen once per treatment cycle (Day 1) during their participation in the active treatment of the study. More frequent follow-up would be only as clinically indicated at the discretion of the treating physician.

Patients will be assessed for disease response and progression. Response will be assessed according to the International Myeloma Working Group (IMWG) criteria (see APPENDIX A) for all patients every 4 weeks for a maximum of 6 cycles (unless disease progression or unacceptable toxicity).

ECOG performance score (APPENDIX B), adverse events (AEs), laboratory values, and vital sign measurements will be collected and assessed throughout the study. Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03, effective date 14 June 2010.

Patients will attend an End of Treatment (EOT) visit after completion of their 6 cycles (or at study discontinuation due to progressive disease, unacceptable toxicity, or other reason) and will continue to be followed for survival.

4.2. Number of Patients

20 patients, male or female, 18 years of age or older, will be enrolled in this study.

4.3. Duration of Study

The duration of this study will be approximately 26 months, including 20 months for enrollment of subjects and approximately 6 months of treatment from the last patient enrolled.

Patients may remain on treatment for a maximum of 6 cycles, unless the occurrence of progressive disease or unacceptable toxicity (or other reason). Patients will continue to be followed for survival.

5. STUDY POPULATION

5.1. Inclusion Criteria

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

- Male or female patients 18 years or older.
- 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.

- 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, 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.)
- 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.)
- Patients must have a diagnosis of relapsed/refractory multiple myeloma and must have received at least one line of prior therapy.
- Eastern Cooperative Oncology Group (ECOG) performance status and/or other performance status 0, 1, or 2.
- Patients must meet the following clinical laboratory criteria:
  - Absolute neutrophil count (ANC) $\geq$ 1,000/mm3 and platelet count $\geq$ 75,000/mm3. Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days before study enrollment.
  - Total bilirubin $\leq 1.5 \times$ the upper limit of the normal range (ULN).
  - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq 3 \times$ ULN.
  - Calculated creatinine clearance $\geq$ 30 mL/min.

5.2. Exclusion Criteria

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

- Patients that have not been previously treated with a multi-drug regimen including a proteasome inhibitor, immunomodulatory drug, and corticosteroid.
- Female patients who are lactating or have a positive serum pregnancy test during the screening period.

- Failure to have fully recovered (ie, ≤ Grade 1 toxicity) from the reversible effects of prior chemotherapy.

- Major surgery within 14 days before enrollment.

- Radiotherapy within 14 days before enrollment. If the involved field is small (in the opinion of the enrolling investigator), 7 days will be considered a sufficient interval between treatment and administration of the ixazomib.

- Patients who have non-myeloma related bone disease that will interfere with the interpretation of the bone-related blood and radiology assessments, including Paget's disease, Rickets, Osteomalacia, and any other metastatic bone cancer.

- History of myeloma-related central nervous system involvement.

- Infection requiring systemic antibiotic therapy or other serious infection within 14 days before study enrollment.

- Evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, symptomatic congestive heart failure, unstable angina, or myocardial infarction within the past 6 months.

- Systemic treatment, within 14 days 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.

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

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

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

- Known GI disease or history of GI procedure that could interfere with the oral absorption or tolerance of ixazomib including difficulty swallowing.

- 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 non-melanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.

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

- Participation in other clinical trials, including those with other investigational agents not included in this trial, within 21 days of the start of this trial and throughout the duration of this trial.

- Patients who have taken bisphosphonate or RANK Ligand Inhibitor within 3 weeks from screening.

6. TREATMENT PLAN

All baseline assessments, labs, and bone marrow biopsies are to be completed within 35 days of enrollment. Radiological studies are to be completed within 60 days prior to enrollment.

Study drug (ixazomib 4.0 mg) will be given on Days 1, 8, 15, 22 of a 28- day cycle for a maximum of 6 cycles.

For a new cycle of treatment to begin, the patient must meet the following criteria:

- ANC must be ≥ 1,000/mm^3.
- Platelet count must be ≥ 75,000/mm^3.
- All other non-hematologic toxicities should, at the investigator's discretion, generally be recovered to patient's baseline condition or Grade 1 or lower.

Dose modifications may be made based on toxicities during treatment described in detail in section 8.2.3. Treatment periods will be defined as 28-day cycles. Patients will be seen in clinic once per treatment cycle (Day 1) during their participation in the active treatment of the study. More frequent follow-up would be only as clinically indicated at the discretion of the treating physician.

Patients will be assessed for disease response and progression. Response will be assessed according to the IMWG criteria (see APPENDIX A) for all patients every 4 weeks for a maximum of 6 cycles (unless disease progression or unacceptable toxicity).

Patients will attend an End of Treatment (EOT) visit after completion of their 6 cycles (or at study discontinuation due to progressive disease, unacceptable toxicity, or other reason) and will continue to be followed for survival. Follow-up for survival after end of treatment will be limited to contact via telephone approximately annually to verify the patient's disposition. Verification of the patient's disposition may be performed by medical record review if the patient was seen in clinic at UAMS within 3 months of the scheduled follow-up interval.

6.1. Physical assessments

Physical Assessments include History and Physical (H&P), which includes a detailed medical and treatment history, vital signs, weight, height, and BSA, and performance evaluation (ECOG) as seen in Appendix B. H&P and performance evaluation will be performed at all visits. Toxicities will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0, effective date 14 June 2010 starting with cycle 1.

6.2. Laboratory tests

Laboratory tests (CBC with differential, BMP, LFTs, Uric Acid, Albumin, CRP, Pregnancy Test (WOCBP)), bone marker tests (BALP, Osteocalcin, NTX, Vitamin D 25), and myeloma lab tests (Serum Protein Electrophoresis, Serum Quantitative Immunoglobulins, Serum Free Light Chains, Serum IFE and/or Urine Beta-2-Microglobulin) will be performed at baseline, on day 1 of cycles 2-6, and at end of study. BNP and TSH will be performed at baseline and end of study only.

6.3. Bone Marrow Tests

Bone marrow aspirate and biopsies will be performed at baseline and at the end of study for immunohistochemistry, cytogenetics, and flow cytometry.

Bone marrow aspirates and biopsies for gene expression profiling (GEP) are optional and will be performed in subjects providing informed consent. Based on the requirement of obtaining at least 3 million plasma cells, approximately 50 ccs of bone marrow aspirate will be collected in a EDTA syringe and sent to the Myeloma Institute Research lab for gene array studies. If there are insufficient plasma cells in the sample to perform gene array, an additional bone marrow pull and bone marrow biopsy may be requested. The sample should be clearly labeled "for separation for GEP for UARK 2014-14".

6.4. Radio-Imaging

The bone densitometry scan (Dexascan) and skeletal survey will be performed at baseline and at end of study.

7. SCHEDULE OF EVALUATIONS

All baseline assessments, labs, and bone marrow biopsies are to be completed within 35 days of enrollment. Radiological studies are to be completed within 60 days prior to enrollment.

	Screening/Baseline	Cycles 1-6	End of Treatment
PHYSICAL ASSESSMENTS			
H&P[1]	X	X	X
Performance Evaluation (ECOG)	X	X	X
Toxicity Evaluation	---	X	X
LABORATORY			
CBC with differential	X	X	X
Basic Metabolic Panel (BMP), Liver Function Tests (LFTs), Uric Acid, Albumin, and CRP [2]	X	X	X
BNP [3]	X	---	X
Pregnancy Test[4] (WOCBPonly)	X	X	X
TSH	X	---	X
BALP, Osteocalcin, NTX	X	X	X
Vitamin D 25	X	X	X
Serum Protein Electrophoresis	X	X	X
Serum Quantitative Immunoglobulins	X	X	X
24 hour urine for total protein, & electrophoresis and calcium	X	X	X
Serum IFE and/or Urine Beta-2-Microglobulin[6]	X	X	X
Serum Free Light Chains	X	X	X
BONE MARROW			
Bone Marrow Aspirate & Biopsy and Gene Expression Profiling[5]	X	---	X
RADIO-IMAGING			
Bone Densitometry (Dexascan)	X	---	X
Skeletal Survey	X	---	X
BANKING FOR FUTURE RESEARCH			
Blood and/or bone marrow[7]	X		

1 History and Physical (H&P) includes a detailed medical and treatment history, vital signs, weight, height, and BSA.
2 BMP includes Na, K, Cl, CO2, BUN, Creatinine, Ca, glucose; LFTs include bilirubin total and direct, SGOT, SGPT, Alkaline phosphatase,

albumin, total protein, and LDH
3 BNP = B-type natriuretic peptide
4 Required while receiving study drug for WOCBP (women of childbearing potential) only
5 BM Aspirate & Biopsy for immunohistochemistry, cytogenetics, and flow cytometry. GEP optional.
6 Upon disappearance of the Urine M and as clinically indicated.
7 Optional blood and/or bone marrow specimens may be collected and stored for future research at any time that sample collection is already required for other tests

8. STUDY DRUG

8.1. Description of Investigational Agent

The ixazomib drug product is provided in strengths of 4.0, 3.0, and 2.3 mg capsules as the active boronic acid. The different dose strengths are differentiated by both capsule size and color as described below:

Dose Strength	Capsule Size	Capsule Color
4.0 mg	Size 4	Ivory
3.0 mg	Size 3	Light gray
2.3 mg	Size 2	Light pink

For additional details, please see the ixazomib IB.

8.2. Study Drug Administration

8.2.1. 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 sub-investigator(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 on 8.2.3 for dose modifications).

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

The prescribed administration of ixazomib doses in this study is 4.0mg ixazomib weekly 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.

8.2.2. Ixazomib Destruction

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

8.2.3. Dose-Modification Guidelines

8.2.3.1. Criteria for Beginning/Delaying Treatment Cycles & Dose Modifications for Treatment Assoc.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 ≥ 1,000/mm^3.
- Platelet count must be ≥ 75,000/mm^3.
- All other non-hematologic toxicities should, at the physician's discretion, generally be recovered to patient's baseline condition or Grade 1 or lower

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 is discontinued is 3 weeks.

8.2.3.2. Ixazomib Dose Adjustment Schedule

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

8.2.3.3. Ixazomib Dose Adjustments for Hematological Toxicities

Ixazomib Dose Adjustments for Hematologic Toxicities

Criteria	Action
Within-Cycle Dose Modifications	
• If platelet count $\leq 30 \times 10^9$/L or ANC $\leq 0.50 \times 10^9$/L on a ixazomib dosing day (other than Day 1)	• Ixazomib dose should be withheld. • Complete blood count (CBC) with differential should be repeated at least every other day until the ANC and/or platelet counts have exceeded the prespecified values (section 8.3.1 above 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 8.3.1 • ANC < 1.0×10^9/L, platelet count < 75×10^9/L, or other nonhematologic toxicities > Grade 1 or not to the patient's baseline condition	• Hold ixazomib until resolution as per criteria Section 8.3.1 • Upon recovery, reduce ixazomib 1 dose level. • The maximum delay before treatment should be discontinued will be 3 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 recover 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 22 dosing thus a dose reduction was not required at that point in the cycle, reduce ixazomib by 1 dose level at the start of the next cycle. o Do not reduce the dose both within a cycle and at the start of the next cycle for the same most severe toxicity.

8.2.3.4. Ixazomib Dose Adjustments for Non-Hematological Toxicities

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

Adverse Event (Severity)	Action on Study Drug	Further Considerations
Peripheral Neuropathy:		
Grade 1 peripheral neuropathy	• 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	• 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 8.2.5	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	• Hold study drug until resolution to Grade < 1 or baseline	Symptomatic recommendations noted in Section 8.2.5
If not recovered to < Grade 1 or baseline within 4 weeks	• Reduce study drug 1 to next lower dose upon return to < Grade 1 or baseline	
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.

8.2.3.5. 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 DDI with a strong inhibitor would increase MLN2238 exposure.
  - 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 to use. A DDI with a strong inducer would decrease MLN2238 exposure.
  - Strong CYP3A inducers: rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, and phenobarbital
  - The dietary supplements St John's wort and Ginkgo biloba are not permitted.
- Additional treatment or procedures prohibited during the study:
  - Adjuvant hormone therapy for breast or prostate cancer.
  - Bisphosphonates: Concomitant treatment with bisphosphonates will not be permitted.
  - Any antineoplastic treatment with activity against MM except for drugs in this treatment regimen.
  - Radiation therapy (the requirement for local radiation therapy generally indicates disease progression).
  - Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days before study drug dosing.

8.2.3.6. 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 Millennium Clinical or Medical

Representative . 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 (except as noted in 8.2.4) and according to institutional guidelines.

- Antiviral therapy such as acyclovir may be administered if medically 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.

8.2.4. Precautions and Restrictions

Fluid deficits should be corrected before and throughout treatment.

Nonsteroidal anti-inflammatory drugs (NSAIDs) induced prevalence of nephrotoxicity is relatively low; however, given the wide use of these agents many persons are at risk, including for example, patients with cardio-renal disease, dehydration, and the aging kidney. 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.)

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.)

8.2.5. 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.

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.

Prophylaxis Against Risk of Infection

If lymphopenia is noted, patients may be at an increased risk of infection. In particular, lymphopenia can be associated with reactivation of herpes zoster and herpes simplex viruses. Antiviral therapy such as acyclovir or valacyclovir may be initiated as clinically indicated. Other antivirals are also acceptable.

Nausea and/or Vomiting

Standard anti-emetics, including 5-HT_3 antagonists, are recommended for emesis occurring upon treatment initiation; prophylactic anti-emetics may also be considered. Dexamethasone should not be administered as an anti-emetic. Fluid deficits should be corrected before initiation of study drug and during treatment.

Diarrhea

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 deficits should be corrected before initiation of treatment and during treatment. Prophylactic antidiarrheals are not generally recommended.

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 ≤ 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. 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

Neutropenia has been reported with ixazomib. 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 with G-CSF according to standard clinical practice. Neutropenic nadirs commonly recover without intervention by the beginning of the next scheduled cycle or with a short delay in treatment. ixazomib administration should be modified when neutropenia occurs, as noted in the dose modification recommendations table. Therapy can be reinitiated at a reduced level upon recovery of absolute neutrophil counts.

Fluid Deficits

Dehydration should be avoided because ixazomib may cause vomiting, diarrhea, and dehydration. Acute renal failure has been reported with ixazomib. Fluid deficits should be corrected before initiation of study drug and during treatment and as needed during therapy. Until further information is available, intake of NSAIDs while on this protocol should be avoided.

Hypotension

Symptomatic hypotension and orthostatic hypotension 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.

Posterior Reversible Encephalopathy Syndrome

One case of posterior reversible encephalopathy syndrome (PRES) has been reported with ixazomib. While this case ultimately resolved, PRES has also been reported rarely with other proteasome inhibitors, VELCADE and Kyprolis. PRES is characterized by headache, seizures and visual loss, as well as abrupt increase in blood pressure. Prompt diagnosis and initiation of antihypertensive and anticonvulsant therapy are important to prevent irreversible end-organ damage.

8.2.6. Preparation, Reconstitution, and Dispensing

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

Packaging and Labeling

The study drug ixazomib capsules will be provided by Millennium. The study drug will be handled as open-label material bearing a label with the following statement: "Caution: New Drug – Limited by Federal Law to Investigational Use."

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

Storage, Handling, and Accountability

Study drug will be stored in the UAMS Research Pharmacy under the supervision of the research pharmacist who will be responsible for maintaining the supply according to the manufacturer's specifications, dispensing the drug for administration, and maintaining all accountability records.

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.

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.

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.

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
- Protocol violation
- Lost to follow-up
- Progressive disease
- Study terminated

At the time of withdrawal, all study procedures outlined for the End of Treatment visit should be completed (unless already completed and withdrawal is only from long-term follow-up for survival). The primary reason for patient's withdrawal from the study should be documented.

9. STATISTICAL AND QUANTITATIVE ANALYSES

9.1. Statistical methods

This is a single-arm, phase 2 study to evaluate bone remodeling during ixazomib treatment in relapsed/refractory MM patients. The primary objective is to evaluate the effect of ixazomib on inducing osteoblast activation as measured by change in osteocalcin from baseline to end of study. Ixazomib will be administered orally at the dosage of 4.0 mg weekly in a 28-day cycle for 6 cycles.

The study parameters of interest are described in Section 3. A similar study outlined in Zangari (16) by Terpos (30) evaluated bone markers after treatment with bortezomib in relapsed myeloma and found marked improvement. Terpos (30) reported the median and range osteocalcin level for myeloma patients at baseline and after 8 cycles of treatment with bortezomib. Based on an observed median osteocalcin level (and estimated standard deviation) of 7.46 ng/ml (sd = 12.65) in baseline myeloma patients compared to 19 ng/ml (sd = 18.6) after treatment with bortezomib, differences in pre- and post-

ixazomib continuous study parameters will be evaluated using a nonparametric Wilcoxon sign-rank test for paired data. The correlation between the pre and post treatment groups is assumed to be 0.5. Using the asymptotic relative efficiency method to define power of a nonparametric test relative to a one sample t test, and a significance level of 0.05, the design gives a power of 88% for 20 patients. If normality assumptions are met, then the paired t-test will be used. Difference in binary study parameters will be evaluated using McNemar's test for correlated proportions. Correlation between bone marker parameters will be evaluated using the Spearman correlation coefficient. One-sided p-values <0.05 will be regarded as statistically significant.

The association between osteoblastic activation and myeloma response to ixazomib and to identify predictive factors for ixazomib-associated osteoblastic activation will be explored using differential expression analysis. All subjects meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response, toxicities, and safety. Baseline and end of study descriptive statistics will be collected and analyzed per the statistical plan.

10. ADVERSE EVENTS

10.1. Definitions

Pretreatment Event Definition

A pretreatment event is any untoward medical occurrence in a patient or subject who has signed informed consent to participate in a study but before administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

Adverse Event Definition

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

With the exception of grade 3-4 laboratory abnormalities, an abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

Serious Adverse Event Definition

- Serious AE (SAE) means any untoward medical occurrence that at any dose:
- Results in death.Is life-threatening (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of an existing hospitalization.
- Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is a medically important event. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical

intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. 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; any organism, virus, or infectious particle (eg, prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

Related

An event is "related" if more likely than not it was caused by the study drug

Unexpected

An event is "unexpected" when its specificity, nature, severity or incidence is not accurately reflected in the consent form, protocol, or IB previously reviewed and approved by the IRB. Examples include lower rate of response to treatment or a side effect that is more severe than initially expected.

Study Period

The study period is defined as the period of time from start of study drug through the End of Treatment visit. Events occurring after enrollment but prior to the study period will be considered pretreatment events (see above).

10.2. Monitoring, Recording and Reporting of AEs

Maurizo Zangari, M.D., is the principal investigator of this study; The University of Arkansas for Medical Sciences (UAMS) is the study sponsor. UAMS is responsible for reporting serious adverse events (SAEs) to any regulatory agency; the principal investigator is responsible for reporting to the IRB and other entities (see Section 10.4).

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. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. All AEs occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. SAEs that are still ongoing at the end of the study period must be followed up for up to 30 days to determine the final outcome. Any SAE that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately to the Sponsor (UAMS).

All subjects will be monitored for AE's during the study. Assessments may include monitoring the patient's clinical symptoms; laboratory, pathological, radiological, or surgical findings; physical examination; or other appropriate tests and procedures.

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).

AE's are to be reported in a routine fashion at scheduled times during the trial, such as with the annual continuing review to the IRB. Certain AEs must be reported in an expedited manner to allow for more timely monitoring of subject safety and care. The preporting of these events depends on the characteristics of the event:

- Seriousness (grading of event)
- Relatedness to study therapy
- Expectedness

Steps to Determine if the event requires expedited Reporting:

- Identify the type of event and grade the event using NCI CTCAE version 4.0
- Determine whether the adverse event is related to the investigational drug. Attribution categories are as follows:
    - Unrelated
    - Unlikely
    - Possible
    - Probable
    - Definite
- Determine the expectedness of the event. Expected events are those previously identified resulting from administration of the agent. See definition for "unexpected" above.

10.3. Expedited Reporting of SAEs

Only adverse events meeting the UPIRTSO (Unanticipated Problem Involving Risks to Subjects or Others) will need to be reported to the UAMS IRB within the required 10 day period of being notified of the event. UPIRTSO requires that an unanticipated problem meet the following qualifications: a) unanticipated or unexpected; b) related to the research; and c) involves new or increased risk to the subject(s). All other adverse events should be recorded and reported to the UAMS IRB at continuing review.

The Sponsor (UAMS) will be promptly notified of all SAEs that are related to the study and unanticipated/unexpected. These SAEs will be reported to the Sponsor using the FDA Medwatch 3500A. UAMS will report events to FDA in accordance with 21CFR312.

All other SAEs will be reported to the Sponsor and FDA in the Annual Progress Report.

Deaths that are related to research will be reported to the Sponsor immediately upon Investigator notification. A death due to a terminal condition of the research participant would be considered anticipated and not related to the research and therefore not immediately reportable under this policy. The sponsor will report deaths to FDA in accordance with 21CFR312.

10.4. Other Required Reporting

AEs which are serious must be reported to Millennium Pharmacovigilance (or designee) from the date the participant signs Informed Consent 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 study 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 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).

Regardless of expectedness or causality, all SAEs (including serious pretreatment events) must also be reported to Millennium Pharmacovigilance:

Fatal and Life Threatening SAEs within 24 hours but no later than 4 calendar days of the investigator's observation or awareness of the event

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

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

The investigator must fax 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): Principal- 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): Principal- 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 4.0, as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.

Relationship to the 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 investigator 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 (if provided by Millennium)
- US FDA MedWatch 3500A: http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm
- Any other form deemed appropriate by the Sponsor and/or Principal Investigator

10.5. Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, or within 90 days of the subject's last dose of study drug she must inform the investigator immediately and permanently discontinue study drug. The investigator must immediately fax a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see above). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the investigator must also immediately fax a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see above). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

11. ADMINISTRATIVE REQUIREMENTS

11.1. 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 1-877-TAKEDA (1-877-825-3327)
Email: medicalinformation@tpna.com
Fax: 1-800-247-8860
Hours: Mon-Fri, 8am-6pm EST

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.

12. ETHICAL AND REGULATORY CONSIDERATIONS

12.1. Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

12.2. Institutional Review

This study must be approved by the UAMS Institutional Review Board, as defined by Federal Regulatory Guidelines (Ref Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

The Investigator will be responsible for preparing documents for submission to the relevant IRB/EC and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study.

Any modifications/amendments to the protocol after receipt of IRB/EC approval must be submitted by the Investigator to the IRB/EC for approval and to the sponsor. The Investigator is also responsible for notifying the IRB/EC and sponsor of any serious deviations from the protocol, or anything that may

involve added risk to study subjects.

12.3. Subject Confidentiality

The Myeloma Institute affirms the subject's right to protection against invasion of privacy. In compliance with United States Federal regulations, representatives of the FDA, NCI and other regulatory authorities may review medical records and copy relevant research records in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

12.4. Investigator Responsibilities

Investigator responsibilities are set out in the ICH guideline for Good Clinical Practice and the Code of Federal Regulations.

The Investigator will permit IRB/EC review and regulatory inspection(s) (e.g. FDA, EMEA, TPP), providing direct access to the facilities where the study took place, source documents and all other study documents.

The Investigator or a designated member of the Investigator's staff must be available at some time during auditing visits to review data and resolve any queries and to allow direct access to the subject's records (e.g. medical records, office charts, hospital charts, and study related charts) for source data verification. All study documents must be made available to the auditing representative so that the accuracy and completeness of study documents may be confirmed.

12.5. Protocol Amendments

If modification of the protocol is necessary, the modification must be confirmed in writing, and the Sponsor will inform the FDA in accordance with 21CFR 312; the Investigator will inform the IRB. Amendments that are administrative in nature do not require IRB approval but will be submitted to the IRB for information.

12.6. Suspension of Study

If conditions arise requiring further clarification before the decision to proceed with or terminate the study can be reached, the study will be suspended until the situation has been resolved.

12.7. Protocol Deviations

When an emergency occurs that requires a deviation from the protocol for a study subject, a deviation will be made only for that subject. The Principal Investigator or other physician in attendance in such an emergency will, if circumstances and time permit, contact the IRB immediately by telephone. If time does not allow for this, the Investigator will notify of the IRB of the deviation as soon as possible in writing.

Such contacts will be made as soon as possible to determine whether or not the subject (for whom the deviation from protocol was effected) is to continue in the study. The subjects' medical and/or research record will completely describe the deviation from the protocol and state the reasons for such deviation.

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APPENDICES

APPENDIX A

Response Criteria and Survival Outcome Definitions

Timing of Response Evaluation

Response will be evaluated according to the Schedule of Evaluations listed above (Section 6.0)

Definition of Measurable Disease

a. Measurable protein criteria of the serum are defined as serum M-protein of IgG, IgA, IgD, IgE Isotype ≥ 1.0 gm/dl (10.0 g/L). Measurable protein criteria of the urine are defined as urine M-protein (Bence-Jones Protein) > 200 mg/24 hours.

b. Participants with IgM peaks must have either ≥ 20% bone marrow plasmacytosis or >3 lytic lesions on skeletal survey.

c. Non-Secretory Disease: Participants without quantifiable M-proteins but with ≥20% bone marrow plasmacytosis will be assessed using plasma cell percentages. These participants will be evaluated for CR, no CR, and progression/relapse using the criteria above.

Response Criteria:

Multiple Myeloma: For the purpose of establishing one set of criteria for both Phase II and Phase III multiple myeloma studies, the following definitions will be used. These definitions are based on the International Uniform Response Criteria for Multiple Myeloma.

a. **Measurable Disease**: Measurable, quantifiable protein criteria must be present. Acceptable protein criteria are:

- Serum M protein ≥ 1 g/dL (≥ 10 g/L), quantified by using densitometry on serum protein electrophoresis (SPEP).

  AND / OR

- Urine M protein [Bence-Jones Protein] ≥ 200 mg/24 hrs (≥ 0.2 g/24 hrs), quantified by 24-hour urine protein electrophoresis (UPEP).

  OR

- Patients who have both serum M protein levels < 1 g/dL AND urine M protein levels < 200 mg/24 hrs at baseline may be followed by serum free light chain (FLC) assay if involved free light chain level ≥ 10 mg/dL (≥ 100mg/L).

Oligosecretory and Non-secretory Disease: Patients that do not meet the criteria for measurable disease above may only be assessed for the following objective statuses: Stringent Complete Response, Stable, and Progression.

b. **Objective Status:**

Stringent Complete Response (sCR):

- Meets all of the criteria for Complete Response (CR) ***and***
- normal serum free light chain ratio ***and***

absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence

Complete Response (CR):

- Disappearance of all evidence of serum and urine M proteins on immunofixation electrophoresis studies ***and***
- ≤ 5% plasma cells in bone marrow ***and***
- disappearance of any soft tissue plasmacytomas

Very Good Partial Response (VGPR):

- Meets all of the criteria for Partial Response (PR) ***and***
- Serum and urine M proteins detectable by immunofixation but not on electrophoresis ***or***
- ≥ 90% reduction in serum M protein **and** urine M protein < 100 mg/24 hrs.

Partial Response (PR):

- If the patient had soft tissue plasmacytomas present at baseline and they were assessed at this disease assessment: ≥ 50% reduction in size of soft tissue plasmacytomas (see Appendix A; Notes h.)***and***
- If the patient had ≥ 30% plasma cells in bone marrow at baseline and a bone marrow biopsy was done: ≥ 50% reduction in plasma cells ***and***
- ≥ 50% reduction in serum M protein **and** reduction in urine M protein ≥ 90% or to < 200 mg/24hr ***or***
- If patient had serum M protein < 1 g/dL, urine M protein < 200 mg/24 hrs, and an involved serum free light chain level ≥ 10 mg/dL at baseline: ≥ 50% decrease in the difference between involved and uninvolved serum free light chain levels

Stable Disease (STA):

- Patient does not meet criteria for Stringent Complete Response, Complete Response, Very Good Partial Response, Partial Response, or Progression.

Progression (PROG): Any one or more of the following:

- Serum M protein increase ≥ 25% from baseline (or an increase of ≥ 1 g/dL if serum M protein was ≥ 5 g/dL at baseline), with an absolute increase of ≥ 0.5 g/dL ***or***
- Urine M protein increase ≥ 25% from baseline, with an absolute increase of ≥ 200 mg/24 hrs ***or***
- If patient had serum M protein < 1 g/dL, urine M protein < 200 mg/24 hrs, and an involved serum free light chain level ≥ 10 mg/dL at baseline: ≥ 25% increase in the difference between involved and uninvolved serum free light chain level, with an absolute increase of ≥ 10 mg/dL ***or***
- Bone marrow plasma cell percentage increase ≥ 25% from baseline, with the absolute plasma cell % ≥ 10% ***or***
- New bone lesions or soft tissue plasmacytomas, or definite increase in size of existing bone lesions or soft tissue plasmacytomas (see Appendix A: Notes h.) ***or***
- Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to multiple myeloma

NOTE: If a disease assessment indicates that a patient is experiencing a Stringent Complete Response, Complete Response, Very Good Partial Response, Partial Response, or Progression, this should be confirmed by a second disease assessment and this should be done prior to the institution of any new therapy. The second disease assessment may be done at any time.

Notes:

a. "M protein" may also be known by the following synonyms: M-spike, monoclonal protein, myeloma protein, monoclonal paraprotein, M-component.

b. Urine M protein measurement is estimated using 24-hour urine protein electrophoresis (UPEP) only. Random or 24 hour urine tests measuring kappa and lambda light chain levels are not reliable and are not recommended.

c. Patients with 'measurable disease' in both the serum and urine (serum M protein ≥ 1g/dL and urine M protein ≥ 200 mg/24h) at baseline need to be followed by both SPEP and UPEP for response assessment.

d. Except for assessment of Complete Response, patients with 'measurable disease' restricted to the serum (serum M

protein ≥ 1 g/dL and urine M protein < 200 mg/24h) at baseline may be followed by SPEP only. Likewise, except for assessment of Complete Response, patients with 'measurable disease' restricted to the urine (serum M protein < 1 g/dL and urine M protein ≥ 200 mg/24h) at baseline may be followed by UPEP only.

e. Patients with serum M protein ≥ 1 g/dL and/or urine M protein ≥ 200 mg/24h at baseline will be assessed for response based on SPEP and/or UPEP results only. Except for assessment of Stringent Complete Response, serum free light chain (FLC) assay response requirements are only applicable to patients who had serum M protein < 1 g/dL, urine M protein < 200 mg/24 hrs, and an involved serum free light chain level ≥ 10 mg/dL at baseline. A normal serum free light chain ratio is required for all patients for a Stringent Complete Response.

f. To qualify for a Complete Response, both serum and urine immunofixation must be carried out and must be negative, regardless of the size of the baseline M protein in the serum or urine.

g. Skeletal survey is not required for assessment of response unless clinically indicated, but is recommended once a year in clinical practice. Stringent Complete Response, Complete Response, Very Good Partial Response, Partial Response, and Stable Disease all require no known evidence of progressive or new bone lesions if radiographic studies were performed, but radiographic studies are not required to satisfy these response requirements.

h. The size of the soft tissue plasmacytomas is defined as the sum of the products of the cross-diameters of each plasmacytoma. The size of the bone lesions will be determined in a similar manner. A definite increase in the size is defined as a ≥ 50% increase (and at least 1 cm^2) of this sum.

Best Response: This is calculated from a sequence of Objective Status evaluations

Stringent Complete Response (sCR): An objective status of Stringent Complete Response on at least two sequential disease assessments. Only one bone marrow biopsy, done during one of these two disease assessments, is required to confirm the response.

Complete Response (CR): An objective status of Complete Response on at least two sequential disease assessments. Only one bone marrow biopsy, done during one of these two disease assessments, is required to confirm the response.

Very Good Partial Response (VGPR): An objective status of Very Good Partial Response on at least two sequential disease assessments.
Partial Response (PR): An objective status of Partial Response on at least two sequential disease assessments.

Unconfirmed sCR (UsCR): One objective status of Stringent Complete Response (based on evidence from serum and urine studies and, if drawn, bone marrow biopsy) but the confirmation studies are either not done, or when done, do not meet the requirements necessary to confirm response. This must be documented before progression and at least three weeks after registration.

Unconfirmed CR (UCR): One objective status of Complete Response (based on evidence from serum and urine studies and, if drawn, bone marrow biopsy) but the confirmation studies are either not done, or when done, do not meet the requirements necessary to confirm response. This must be documented before progression and at least three weeks after registration.

Unconfirmed VGPR (UVGPR): One objective status of Very Good Partial Response, but the confirmation studies are either not done, or when done, do not meet the requirements necessary to confirm response. This must be documented before progression and at least three weeks after registration.

Unconfirmed PR (UPR): One objective status of Partial Response, but the confirmation studies are either not done, or when done, do not meet the requirements necessary to confirm response. This must be documented before progression and at least three weeks after registration.

Stable / No Response (STA): At least one objective status of Stable at least three weeks after registration, but not qualifying as any of the above. If radiographic studies were performed there should be no known progressive or new bone lesions.

Increasing Disease (INC): First objective status recorded (other than Unknowns or those before three weeks) of Progression, provided this occurs within eight weeks of registration.

Inadequate Assessment. Response Unknown (NASS): Progression greater than eight weeks after registration and either all objective statuses prior to registration are unknown or the only known objective statuses occurred less than three weeks after registration.

Relapse**:** In patients with a confirmed response as described above, relapse is defined as the first occurrence of any of the following, reconfirmed by repeat analysis of serum and/or 24-hour urine M protein, done more than 2 weeks apart:

a. Myeloma protein increase by more than 100% from the lowest level recorded on study, or a rise of 2.0 g/dl (this increase must be to a level > 1.0 g/dL if it is to constitute the sole manifestation of relapse).
b. Myeloma protein increase above the response criteria for PR (see criteria for Partial Remission).
c. Reappearance of M-protein in blood or urine not related to immune recovery or recent infection.
d. Increase in the size and number of lytic bone lesions recognized on radiographs. New skeletal or MRI lesions, preferentially confirmed by fine needle aspirate.
e. Myeloma related cytogenetic abnormalities.
f. BM plasmacytosis > 10% or > 5% light chain restricted, non-diploid, plasma cells on cIg/DNA.
g. Hypercalcemia, not explained by any other cause.

Survival Outcomes

Overall Survival: measured as the time from initial registration to death from any cause.

Event-Free Survival: measured as the time from initial registration to progression/relapse of disease or death from any cause

APPENDIX B

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.

APPENDIX C

Diagnostic and Staging Criteria

Diagnostic Criteria

Revised IMWG Diagnostic Criteria for Multiple Myeloma (Rajkumar, et al, 2014)

Clonal bone marrow plasma cells ≥ 10% or biopsy-proven bony or extramedullary plasmacytoma[a]
 	
And any one or more of the following myeloma defining events:
 	
• Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
  ○ Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the ULN or >2.75 mmol/L (>11 mg/dL)
  ○ Renal insufficiency: CrCl <40 mL per min[b] or SCr >177 µmol/L (>2 mg/dL)
  ○ Anemia: Hb >20 g/L below the LLN, or Hb <100 g/L
  ○ Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT[c]
 	
• Any one or more of the following biomarkers of malignancy:
  ○ Clonal bone marrow plasma cell percentage[a] ≥60%
  ○ Involved:uninvolved serum FLC ratio[d] ≥100
  ○ >1 focal lesions on MRI studies[e]

CrCl, Creatinine clearance; CT, computed tomography; FLC, free light chain; Hb, hemoglobin; Ig, immunoglobulin; IMWG, International Myeloma Working Group; LLN, lower limit of normal; M protein, monoclonal protein; MRI, magnetic resonance imaging; PET-CT, Positron emission tomography-computed tomography; ULN, upper limit of normal; SCr, serum creatinine [a]Clonality should be established by showing κ/λ –light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used. [b]Measured or estimated by validated equations. [c]If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement. [d]These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥100 mg/L. [e]Each focal lesion must be 5 mm or more in size.

Staging Criteria

International Staging system [ISS]

New International Staging System (Greipp, et al, JCO 2005)		
Stage	Criteria	Median Survival (months)
I	Serum β2-microglobulin < 3.5mg/L Serum Albumin ≥ 3.5 g/dL	62
II	Not stage I or III	44
III	Serum β2-microglobulin > 5.5 mg/L	29
**There are two categories for stage II: serum β2-microglobulin < 3.5 mg/L but serum albumin < 3.5 g/dL; or serum β2-microglobulin 3.5 to < 5.5 mg/L irrespective of the serum albumin level.*		