Protocol Version 9 Date: September 13, 2017

NCI Protocol #*:* N/A

Local Protocol #:
(Millennium #X16057)

Title:

Phase II Trial of ixazomib, dexamethasone and rituximab in patients with untreated Waldenstrom's Macroglobulinemia.

Principal Investigator:

Jorge J. Castillo, MD
Email: jorgej_castillo@dfci.harvard.edu

Coordinating Center:

Bing Center for Waldenstrom's Macroglobulinemia
Dana-Farber Cancer Institute
450 Brookline Ave.
Boston, MA 02215

Co-Investigators:

Steven P. Treon, MD, PhD
Dana-Farber Cancer Institute
450 Brookline Ave.
Boston, MA 02215

Statistician:

Katherine Kacena, Ph.D.
66 Speen Street
Natick, MA 01760
Tel: 508-808-4383
Email: kk@kkstats.com

Responsible Nurse Practitioner:

Toni Dubeau, NP
Bing Center for Waldenstrom's Macroglobulinemia
Dana-Farber Cancer Institute
450 Brookline Ave.
Boston, MA 02215
Tel: 617-632-3685

Fax: 617-582-9982
Email: toni_dubeau@dfci.harvard.edu

Study Coordinator:

Kirsten Meid
Bing Center for Waldenstrom's Macroglobulinemia
Dana-Farber Cancer Institute
450 Brookline Ave.
Boston, MA 02215
Tel: 617-632-5598
Fax: 617-582-9982
E-mail: Kirsten_meid@dfci.harvard.edu

Responsible Data Manager:

Kirsten Meid
Bing Center for Waldenstrom's Macroglobulinemia
Dana-Farber Cancer Institute
450 Brookline Ave.
Boston, MA 02215
Tel: 617-632-5598
Fax: 617-582-9982
E-mail: Kirsten_meid@dfci.harvard.edu

Agents: Ixazomib, Rituximab, Dexamethasone

This is an investigator-initiated study. The principal investigator Jorge J. Castillo, MD (who may also be referred to as the sponsor-investigator), is conducting the study and acting as the sponsor. Therefore, the legal/ethical obligations of the principal investigator include both those of a sponsor and those of an investigator.

SCHEMA

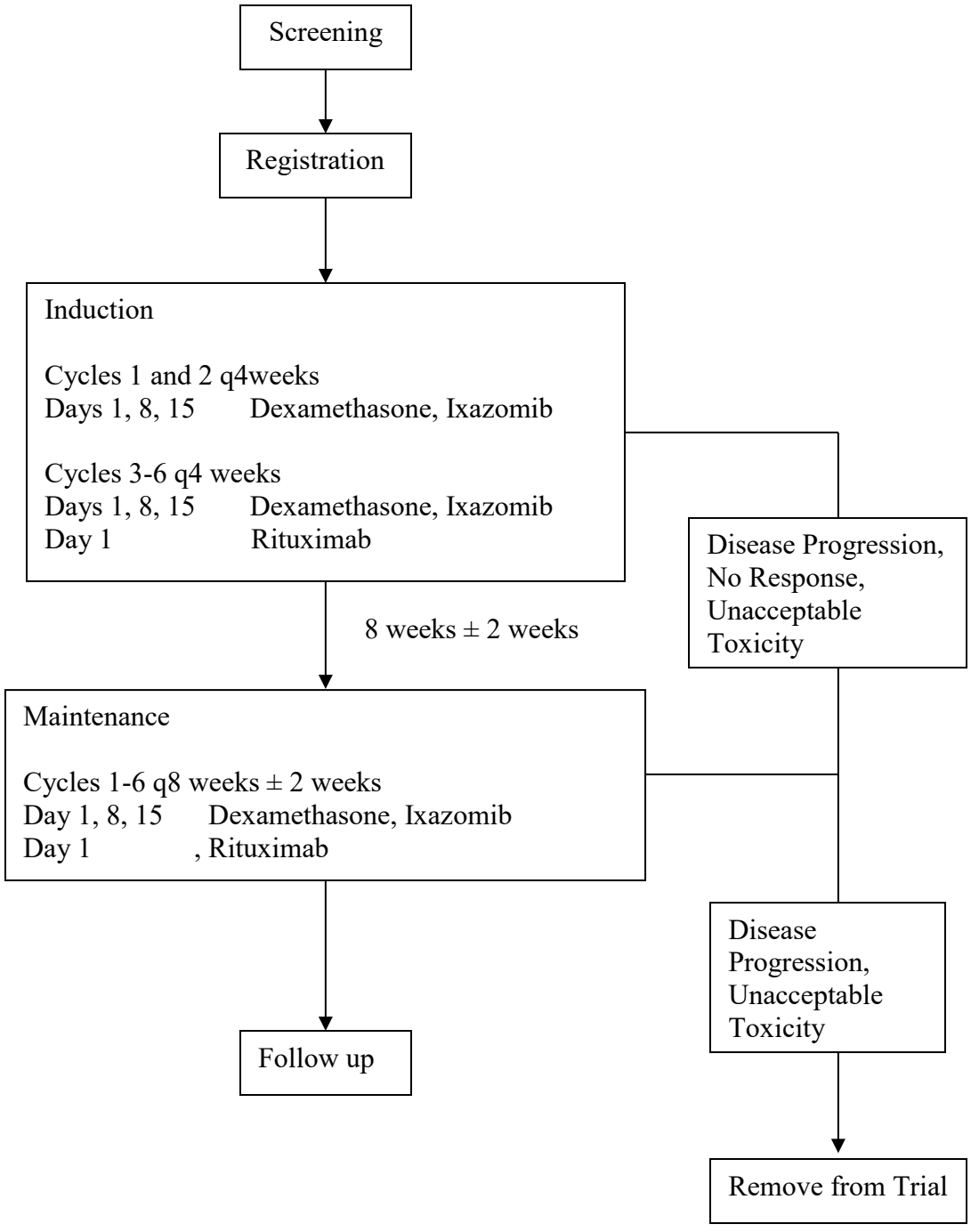

Screening
Registration
Induction
Cycles 1 and 2 q4weeks
Days 1, 8, 15 Dexamethasone, Ixazomib
Cycles 3-6 q4 weeks
Days 1, 8, 15 Dexamethasone, Ixazomib
Day 1 Rituximab
8 weeks ± 2 weeks
Maintenance
Cycles 1-6 q8 weeks ± 2 weeks
Day 1, 8, 15 Dexamethasone, Ixazomib
Day 1 , Rituximab
Follow up
Disease Progression, No Response, Unacceptable Toxicity
Disease Progression, Unacceptable Toxicity
Remove from Trial

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
$5\text{-}HT_3$	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
CR	complete response
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}

Abbreviation	Term
DDI	drug-drug interaction
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
ICF	informed consent form
ICH	International Conference on Harmonisation
IDR	Ixazomib, dexamethasone, rituximab
IEC	independent ethics committee
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous; intravenously
IVRS	interactive voice response system
K_i	inhibition constant
KPS	Karnofsky Performance Status
LDH	lactate dehydrogenase
LFT	liver function test(s)
MedDRA	Medical Dictionary for Regulatory Activities
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MRI	magnetic resonance imaging

Abbreviation	Term
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)
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
QOD	*quaque altera die*; every other day
QOL	quality of life
QTc	rate-corrected QT interval (millisec) of electrocardiograph
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SC	Subcutaneous
SD	stable disease
SmPC	Summary of Product Characteristics
$t_{1/2}$	terminal disposition half-life
TGI	tumor growth inhibition
T_{max}	single-dose time to reach maximum (peak) concentration
UK	United Kingdom
ULN	upper limit of the normal range
US	United States
V_z	volume of distribution in the terminal phase
WBC	white blood cell
WHO	World Health Organization
WM	Waldenström Macroglobulinemia

1. OBJECTIVES

1.1Study Design

This is a single-arm, open-label, prospective phase II study to evaluate the safety and efficacy of IDR in symptomatic untreated WM patients. The study treatment will consist on an induction and a maintenance phase. Dose modification will be permitted for toxicity.

IDR Induction:
Cycles 1 and 2 will consist on ixazomib 4 mg and dexamethasone 20 mg IV or PO administered on days 1, 8 and 15.
Cycles 3-6 will consist on ixazomib 4 mg PO and dexamethasone 20 mg IV or PO on days 1, 8 and 15, and rituximab 375 mg/m^2 IV on day 1 every 28 days.
Total duration of induction: 24 weeks.

IDR Maintenance:
Maintenance therapy will start 2 months ± 2 weeks after day 1 of cycle 6 and will consist on ixazomib 4 mg PO and dexamethasone 20 mg IV or PO administered on days 1, 8 and 15, and and rituximab 375 mg/m^2 IV administered on day 1 every 2 months for 1 year (6 cycles).
Total duration of maintenance: 52 weeks.

Supportive therapy:
Acyclovir 400 mg PO BID or Valacyclovir 1000mg PO QD will start on day 1 of study and will continue for 6 months after the last dose of ixazomib.
Famotidine 20 mg PO (or other gastritis prophylactic medication) will start on day 1 of study and will continue until the last dose of dexamethasone.
Acetaminophen 650 mg PO, diphenhydramine 50 mg PO and famotidine 20mg IV will be administered at least 30 minutes prior to each rituximab infusion.

A Screening visit will be conducted within 30 days before baseline (baseline being Day 1, Cycle 1, before study drug administration). At this visit, a medical history will be obtained with complete physical examination, vital signs, and an ECOG performance status. A bone marrow aspirate and biopsy, beta-2-microglobulin, serum and protein electrophoresis with quantification of immunoglobulins (IgM, IgG, IgA) and immunofixation studies, and computed tomography (CT) scans of the chest, abdomen and pelvis will also be conducted at the Screening visit. Bone marrow biopsy and CT scans will not be required if collected up to 90 days prior to screening visit. MYD88 L265P mutational status will be determined by BWH Molecular Diagnostics Lab. CXCR4 mutational status and FcγRIIIA-158 polymorphisms will be determined by the Bing Center for Waldenström Macroglobulinemia Laboratory. Clinical laboratory tests including a complete blood count plus differential, electrolytes, BUN, creatinine, comprehensive chemistry panel, magnesium, total bilirubin, liver function tests, and serum pregnancy tests for women of child-bearing potential will also be performed at the Screening visit.

Patients who meet the eligibility requirements at the Screening visit, and provide written consent, will be enrolled in the study and initiated on study treatment. Patients will be evaluated for

tolerance and response on Day 1 of each cycle for the duration of the trial. Patients will be eligible to continue therapy as long as they do not demonstrate progressive disease or unacceptable toxicity. Modified response criteria updated at the Sixth International Workshop on WM (Owen 2013) will be used to assess response, stable disease, and progressive disease. Response outcomes to be determined will include: ORR and major response rates (including VGPR and CR rates); landmark analysis for 2 and 4-year PFS; median TTP; median TTNT. The final analysis will be undertaken when all participants would have completed the maintenance phase of the study.

1.2Primary Objectives

- To evaluate the rate of very good partial response (VGPR) or better to IDR in patients with untreated WM
- To evaluate the toxicity profile of IDR in patients with untreated WM

1.3Secondary Objectives

- To evaluate the rate of CR, partial response (PR), minimal response (MR), stable disease (SD) and progressive disease (PD)
- To evaluate the PFS, disease-free survival (DFS), time to progression (TTP), duration of response (DOR) and time to next therapy (TTNT)
- To evaluate the attainment of response, and depth of response (VGPR or better) and expression of MYD88 L265P and CXCR4-WHIM mutations in WM.
- To determine changes in MYD88 L265P burden in response to IDR in patients with WM using real-time quantitative PCR.
- To evaluate the FcγRIIIA-158 polymorphisms as surrogate markers for response to IDR in WM.

2.BACKGROUND

2.1Study Agents

2.1.1Ixazomib

2.1.1.1Ixazomib Background

Ixazomib is a next generation, small molecule inhibitor of the 20S proteasome that is under development for the treatment of non-hematologic malignancies, lymphoma, multiple myeloma (MM), and other plasma cell dyscrasias. Inhibition of the 20S proteasome has been validated as a therapeutic target for the treatment of malignancies using VELCADE® (bortezomib) for Injection, Millennium Pharmaceuticals' first-in-class proteasome inhibitor.

In an effort to broaden activity against a wider range of tumor types and increase activity in tumor types where VELCADE has shown activity, Millennium has developed the proteasome inhibitor, Ixazomib, formulated for both intravenous (IV) and oral (PO) administration. Ixazomib is structurally different from VELCADE. MLN2238 refers to the biologically active, boronic

acid form of the drug substance, Ixazomib. Ixazomib refers to the citrate ester of MLN2238. In water or aqueous systems, the equilibrium shifts from Ixazomib to form MLN2238. All doses and concentrations are expressed as the boronic acid, MLN2238.

2.1.1.2 Ixazomib Toxicology Studies

After PO administration of MLN2238, the exposures that were tolerated in rats were similar to those tolerated in dogs, indicating similar species sensitivity. Additionally, PO administration for 5 cycles to rats and dogs resulted in higher plasma exposures of MLN2238 on Day 94 than on Day 0, indicating accumulation of MLN2238. Dose-limiting toxicity (DLT) in the GLP-compliant PO toxicology studies up to 5 cycles in duration in rat and dogs was primarily due to effects in the gastrointestinal (GI) and lymphoid systems. Additionally, at doses below those associated with DLT, alterations in leukocyte and coagulation parameters consistent with an inflammatory response were seen in both rats and dogs, and neuronal degeneration of the sympathetic, dorsal root, and end organ ganglia was seen mainly in dogs (possibly due to higher exposures). All of the effects seen in the GLP-compliant PO toxicology studies in both rats and dogs at tolerated doses were reversible/reversing and can be monitored in the clinic with routine clinical observations (GI disturbances and opportunistic infections secondary to lymphoid depletion), clinical pathology assessments (inhibition of erythropoiesis, thrombocytopenia, and inflammatory leukogram), and neurologic assessment, as are commonly done for patients treated with bortezomib. Ixazomib did not cause significant toxicities that have not been previously observed after dosing with bortezomib, and the neurologic lesions in these studies are similar to what has been described after treatment with bortezomib and are believed to be the cause of the peripheral neuropathy observed in patients treated with bortezomib.

MLN2238 caused embryo-fetal toxicity to pregnant rabbits at a dose of 1 mg/kg (mean Gestation Day 19 $AUC_{0\text{-}72hr}$ □ 1280 hr*ng/mL). Embryo-fetal toxicity has been observed in rats and rabbits with other proteasome inhibitors, and thus there is the potential for similar effects in humans. A dose of 0.5 mg/kg (mean Gestation Day 19 $AUC_{0\text{-}72hr}$ □ 910 hr*ng/mL) was considered the no-observed-effect level (NOEL) for embryo-fetal effects in this study.

MLN2238 was not mutagenic in a GLP-compliant bacterial reverse mutation assay (Ames assay) nor was it clastogenic in a GLP-compliant bone marrow micronucleus assay in mice. Therefore, MLN2238 is not a genotoxicant.

Ixazomib demonstrates minimal to no absorbance between 290 to 700 nm, and there is no absorption maximum in that range. In a quantitative whole body autoradiography (QWBA) study, [^{14}C] Ixazomib -derived radioactivity was present in melanin-containing tissues (eg, pigmented skin and eye uveal tract), but the concentrations decreased in a manner similar to most other tissues throughout the study and so a specific association of radioactivity to melanin was not obvious. The data indicate that Ixazomib does not represent a photosafety risk.

2.1.1.3 Ixazomib Preclinical Antitumor Activity

Ixazomib is a next generation proteasome inhibitor. Its active form, MLN2238, is a potent, reversible, and selective inhibitor of the □5 site of the 20S proteasome. MLN2238 inhibits the

□5 site 20S proteasome activity in vitro, with a concentration producing IC_{50} of 3.4 nM. Potency is reduced roughly 10-fold versus □1 (IC_{50} □ 31 nM) and 1000-fold versus □2 (IC_{50} □ 3500 nM). MLN2238 was also tested for inhibition against a panel of 103 kinases, 18 receptors (neurotransmitter, ion channel, brain and gut receptors), and 9 serine proteases. In all cases, the IC_{50} was □ 10 □M. Proteasome inhibition results in the accumulation of poly-ubiquitinated substrates within the cell and leads to cell cycle disruption, with concomitant activation of apoptotic pathways and cell death. Consistent with inhibition of □5 20S proteasome activity, MLN2238 demonstrated potent activity against cultured MDA-MB-231 human breast cancer cells in the WST cell viability assay.

The iMyc□/Bcl-X_L GEM model of PCM recapitulates key features of human MM, including elevation of serum paraprotein, manifestation of malignant plasma cells in bone marrow, and involvement of osteolytic lesions. iMyc□/Bcl-X_L mice of C57BL6/FVB background develop de novo PCM accompanied by splenomegaly. This model was used to assess the anti-tumor activity of bortezomib and MLN2238. In addition, the anti-tumor activity of bortezomib and MLN2238 was evaluated in a disseminated model of PCM in immunocompromised mice and in an intratibial model of PCM in nude mice. These 2 models utilized the DP54-Luc cell line, a luciferase-tagged cell line derived from a tumor originating in an iMyc□/Bcl-X_L transgenic mouse.

Study CPPI-09-EF29

Male and female iMyc□/Bcl-X_L mice of the hybrid (B6 □ FVB/N) F_1 background were administered bortezomib at 1.2 mg/kg IV BIW or MLN2238 at 18 mg/kg IV BIW for 6 consecutive weeks (treatment phase) (n □ 30), with an untreated group as a control. The doses used represent the MTD for each drug in (B6 □ FVB/N) F_1 hybrid mice. After the treatment phase, mice were clinically monitored for an additional 25 weeks to assess the effect of drug treatment on overall survival, spleen weight, and plasma immunoglobulin G2a (IgG2a) levels (a marker for myeloma disease). The results of this study showed that IV BIW administration of MLN2238 at 18 mg/kg and bortezomib at 1.2 mg/kg prolonged overall survival, reduced splenomegaly, and attenuated IgG2a levels in the iMyc□/Bcl-X_L GEM model of de novo PCM.

Study CPPI-09-EF26

Female NOD-SCID mice bearing disseminated DP54-Luc iMyc□/Bcl-X_L PCM were dosed with vehicle (5% hydroxypropyl-beta-cyclodextrin [HP-□-CD]) IV BIW, bortezomib at 0.7 mg/kg IV BIW, MLN2238 at 11 mg/kg IV BIW, or MLN2238 at 3 mg/kg SC QD. The doses used represent the MTD for each drug and route of administration in NOD-SCID mice. A total of 5 doses were administered in the IV dose groups and a total of 15 doses were administered in the SC dose group. Anti-tumor activity was determined by calculating the T/C ratio of the mean total photon flux measurement of tumor burden on Day 20 after inoculation. In addition, cranial suture widening was assessed on Day 23 after inoculation in the IV dose groups by measuring sagittal suture separation areas (SSSA) using computed tomography (CT) imaging.

The results of this study demonstrated that bortezomib and MLN2238 show anti-tumor activity against DP54-Luc iMyc□/Bcl-X_L PCM. Importantly, IV MLN2238, but not bortezomib,

significantly reduced osteolytic lesions (widening of cranial sutures) in this model.

Study CPPI-09-EF27

Female nude mice bearing intratibial DP54-Luc iMyc□/Bcl-XL PCM were dosed IV BIW with vehicle (5% HP-□-CD), bortezomib at 0.8 mg/kg, or MLN2238 at 13 mg/kg for 3 consecutive weeks. Anti-tumor activity was determined by calculating the T/C ratio of the mean photon flux measurement of tumor burden on Day 29 after inoculation.

The results of this study demonstrated that bortezomib and MLN2238 show anti-tumor activity against intratibial DP54-Luc iMyc□/Bcl-XL plasma cell malignancy.

2.1 Pharmacokinetics and Drug Metabolism

Clinical IV and PO PK data show that ixazomib citrate (measured as the biologically active boronic acid form of ixazomib [MLN2238]) has multi-exponential disposition with a rapid initial phase that is largely over by 4 hours. Oral ixazomib citrate is rapidly absorbed with a median single-dose first time of occurrence of maximum (peak) concentration (T_{max}) of approximately 0.5 to 2.0 hours and a terminal disposition half-life ($t_{1/2}$) after multiple dosing of approximately 5 to 7 days [1]. Results of a population PK analysis (n = 137) show that there is no relationship between body surface area (BSA) or body weight and clearance (CL). Also, based on stochastic simulations for fixed dose, exposures are independent of the individual patient's BSA [2]. Based on these data, a recommendation was made for fixed dosing in clinical trials. An absolute bioavailability of 67% was determined for ixazomib using the population PK analysis. Please refer to the current ixazomib IB and Safety Management Attachment (SMA) for information on the PK for IV doses of ixazomib.

Metabolism appears to be the major route of elimination for ixazomib, and urinary excretion of the parent drug is negligible (< 5% of dose). In vitro studies indicate that ixazomib is metabolized by multiple cytochrome P450s (CYPs) and non-CYP enzymes/proteins. The rank order of relative biotransformation activity of the 5 major human CYP isozymes was 3A4 (34.2%) > 1A2 (30.7%) > 2D6 (14.7%) > 2C9 (12.1%) > 2C19 (< 1%). Ixazomib is not an inhibitor of CYPs 1A2, 2C9, 2C19, 2D6, or 3A4 nor a time-dependent inhibitor of CYP3A4/5. The potential for ixazomib treatment to produce drug-drug interactions (DDIs) via CYP inhibition is inferred to be low. However, there may be a potential for DDIs with a concomitant strong CYP3A4 or CYP1A2 inhibitor or inducer because of the potential for first-pass metabolism when ixazomib is administered via the PO route and because of the moderate contribution of CYP3A4- and CYP1A2-mediated metabolism of ixazomib in human liver

microsomes. Ixazomib may be a weak substrate of P-glycoprotein (Pgp), breast cancer resistance protein (BCRP), and multidrug resistance associated protein (MRP2) efflux pump transporters. Ixazomib is not an inhibitor of Pgp, BCRP, and MRP2. The potential for DDIs with substrates or inhibitors of Pgp, BCRP, and MRP2 is, therefore, inferred to be low. Clinical Study C16009 (Arm 1) with ketoconazole, a strong CYP3A4 inhibitor, showed a 2-fold increase in area under the plasma concentration versus time curve (AUC) in the presence of ketoconazole. This resulted in the continued exclusion of strong CYP3A4 inhibitors in ongoing/planned clinical studies.

Further details on these studies are provided in the IB.

Preclinical Experience

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

2.1.1.1 Clinical Experience with Ixazomib

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

As of 27 March 2013, preliminary clinical data is available for a total of 653 patients across 13 studies. The emerging safety profile indicates that ixazomib is generally well tolerated. The adverse events (AEs) are consistent with the class-based effects of proteasome inhibition and are

similar to what has been previously reported with VELCADE though the severity of some, for example peripheral neuropathy, is less. While some of these potential toxicities may be severe, they can be managed by clinical monitoring and standard medical intervention, or, as needed, dose modification or discontinuation.

Fatigue was the most common AE reported among 384 patients treated in the oral (PO) studies (47%). Other common AEs reported in the pooled intravenous (IV) and PO safety populations include nausea, thrombocytopenia, diarrhea, and vomiting. Rash is also a commonly reported treatment-emergent event; however, there is some variety in its characterization and causality resulting in different preferred terms to describe it. A high-level term outline of rash events includes rashes, eruptions and exanthems NEC; pruritus NEC; erythemas; papulosquamous conditions; and exfoliative conditions. The dose escalation phases of most trials reported in the IB have now completed enrollment, and gastrointestinal (GI) symptoms were the common dose-limiting toxicities (DLTs) when the use of prophylactic anti-emetics was not permitted per protocol. In the expansion cohorts or phase 2 cohorts (as per each study), the incidence and severity of GI symptoms was mitigated by the use of the lower maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) (as per each study) and standard clinical usage of anti-emetics and/or antidiarrheal medications as deemed appropriate. Prophylactic use of anti-emetics has not been required as with other agents but (as outlined in Section 6.7) has been used according to standard practice and are effective.

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

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

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 1-1.

Table 1-1 Clinical studies of Oral Ixazomib

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

Table 1-1 Clinical studies of Oral Ixazomib

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

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

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

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

2.1.1.2 Clinical Experience with Ixazomib as Monotherapy

The C16003 study was a phase 1 study in adult patients with relapsed and/or refractory MM who had received at least 2 lines of prior therapy that must include Velcade, thalidomide or

lenalidomide) and steroids. This study enrolled 60 out of 63 planned participants and is closed to accrual. Ixazomib was administered twice weekly on days 1, 4, 8 and 11 of a 21-day cycle and underwent dose escalation from 0.24 mg/m2 to 2.23 mg/m2. The MTD for twice weekly ixazomib was determined at 2.0 mg/m2.

The C16004 study was a phase 1 study in adult patients with relapsed and/or refractory MM who had received at least 2 lines of prior therapy that must include Velcade, thalidomide or lenalidomide) and steroids. This study enrolled 60 out of 70 planned participants and is closed to accrual. Ixazomib was administered once weekly on days 1, 8 and 15 of a 28-day cycle with dose escalation from 0.24 mg/m2 to 3.95 mg/m2. The MTD for weekly ixazomib was determined at 2.97 mg/m2.

The C16009 study is an ongoing phase 1 study in adult patients with non-hematologic malignancy or lymphoma. The primary objectives are to evaluate safety, bioavailability, DDI and food effect. There are four arms evaluating ixazomib at different dosages and in combination with ketoconazole and rifampin. The study has enrolled 57 out of 90 planned participants.

2.1.1.3 Experience with Ixazomib in Combination with Lenalidomide and Dexamethasone

The C16005 study is a phase 1/2 study in adult patients with newly diagnosed MM. The objectives of the phase 1 component are safety, MTD and inform RP2D. The objective of the phase 2 component is efficacy. Ixazomib is administered once weekly on days 1, 8 and 15 with dose escalation from 1.68 mg/m2 to 3.95 mg/m2. Ixazomib was administered in combination with dexamethasone 40 mg PO on days 1, 8, 15 and 22, and lenalidomide 25 mg PO on days 1-21 of 28-day cycles for 12 cycles. This is followed by maintenance therapy with ixazomib on days 1, 8 and 15 every 28 days until disease progression or unacceptable toxicity. The MTD of ixazomib was 2.97 mg/m2 and the RP2D is a fixed dose of 4.0 mg (approximate equivalent to 2.23 mg/m2) with full-dose lenalidomide and dexamethasone. This study enrolled 65 participants and is currently closed to accrual.

2.1.1.4 Dose Rationale

After oral dosing, MLN2238 is rapidly absorbed with a median T_{max} of 1 hour. The observed range for the terminal half-life after multiple doses is 2.1 to 11.3 days. Dose proportionality has been observed for doses between 0.48 and 3.95 mg/m^2 (0.8-8.9 actual administered dose range) of Ixazomib. The 2-fold increase in AUC observed in the presence of ketoconazole, a strong inhibitor of CYP3A (Study C16009), resulted in the continued exclusion of strong CYP3A4 inhibitors in ongoing/planned studies.

Pharmacokinetic parameters for MLN2238 co-administered with lenalidomide and dexamethasone (Studies C16005 and C16008), or melphalan and prednisone (Study C16006), appear to be similar to those observed when Ixazomib is administered as a single agent. This suggests that there is no readily apparent effect of co-administration of lenalidomide and dexamethasone, or melphalan and prednisone, on the clinical PK of MLN2238. Likewise, no significant alterations in the disposition of MLN2238 have been noted between patients with different malignancies.

Following either oral administration of ixazomib, maximal 20S proteasome inhibition in blood is observed shortly after dosing, mirroring the obtainment of maximum plasma concentrations of MLN2238. Maximum inhibition of 20S proteasome activity is dose dependent with mean values approaching 70% to 80% in some of the higher dosing cohorts examined. With the exception of some of the higher dosing cohorts studied, prolonged 20S proteasome inhibition (> 96 hours) by Ixazomib is not observed. These findings are consistent with MLN2238 being a reversible proteasome inhibitor.

A population PK analysis has been performed using preliminary PK data from 137 patients treated with IV and PO Ixazomib as a single agent across 4 ongoing, phase 1 studies intensive PK sampling). Patients with solid tumors, lymphoma, or MM were administered Ixazomib via IV or PO routes using BSA-based dosing on a twice weekly (Days 1, 4, 8, and 11; 21-day cycle) or weekly (Days 1, 8, and 15; 28-day cycle) schedule. Effects of age, body weight, BSA, sex, creatinine clearance, ALT, AST, and bilirubin were not significant on the CL of Ixazomib on the basis of a univariate analysis ($p < 0.05$). Because MLN2238 was dosed on the basis of BSA in the early phase 1 clinical studies, it was of interest to see if any of the body size covariates (weight or BSA) were significant on CL or V2. On the basis of the univariate testing, neither weight nor BSA was significant on CL or V2 suggesting that interpatient variability in BSA does not contribute to MLN2238 PK variability.

The lack of a discernible relationship between BSA and Ixazomib clearance over a relatively wide BSA range (1.4-2.6 m^2) indicates that total systemic exposure (AUC) following fixed dosing should be independent of the individual patient's BSA. Therefore, BSA is not expected to affect C_{max} or AUC after IV or oral dosing, and thus fixed dosing is appropriate for both oral and IV routes of administration. The clinical development of Ixazomib has therefore transitioned from the use of BSA-based dosing to fixed dosing in all recently initiated phase 1/2 studies (Studies C16005 phase 2, C16007, C16008, and C16009). Accordingly, the starting dose of Ixazomib in the proposed phase 3 study in relapsed/refractory multiple myeloma is a fixed dose of 4.0 mg, on the basis of the recommended dose of 2.23 mg/m^2 (using mean patient BSA of 1.86 m^2 from the 2208 patients with MM in VELCADE clinical studies for conversion to a fixed dose). Also, no relationship between creatinine clearance and CL was observed in patients with a wide range of renal function (creatinine clearance range: 21.9-236.1 mL/min) as shown in So, starting dose adjustment is not required in patients with mild (60-90 mL/min) and moderate (30-60 mL/min) renal impairment in clinical studies.

2.1.1.5 Overview of the Oral Formulation of ixazomib

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

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

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

Primary System Organ Class Preferred Term	Primary System Organ Class Preferred Term
Subjects with at Least One Adverse Event	Subjects with at Least One Adverse Event
Gastrointestinal disorders	Gastrointestinal disorders
Nausea	Nausea
Diarrhoea	Diarrhoea
Vomiting	Vomiting
Constipation	Constipation
Abdominal pain	Abdominal pain
General disorders and administration site conditions	General disorders and administration site conditions
Fatigue	Fatigue
Pyrexia	Pyrexia
Oedema peripheral	Oedema peripheral
Asthenia	Asthenia
Nervous system disorders	Nervous system disorders
Headache	Headache
Dizziness	Dizziness
Neuropathy peripheral	Neuropathy peripheral
Metabolism and nutrition disorders	Metabolism and nutrition disorders
Decreased appetite	Decreased appetite
Dehydration	Dehydration
Blood and lymphatic system disorders	Blood and lymphatic system disorders

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

Primary System Organ Class Preferred Term	Primary System Organ Class Preferred Term
Thrombocytopenia	Thrombocytopenia
Anaemia	Anaemia
Neutropenia	Neutropenia
Lymphopenia	Lymphopenia
Skin and subcutaneous tissue disorders	Skin and subcutaneous tissue disorders
Rash macular[a]	Rash macular[a]
Musculoskeletal and connective tissue disorders	Musculoskeletal and connective tissue disorders
Back pain	Back pain
Arthralgia	Arthralgia
Respiratory, thoracic and mediastinal disorders	Respiratory, thoracic and mediastinal disorders
Cough	Cough
Dyspnoea	Dyspnoea
Infections and infestations	Infections and infestations
Upper respiratory tract infection	Upper respiratory tract infection
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.	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.
Table 1-2 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Single-Agent Studies	Table 1-2 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Single-Agent Studies
Primary System Organ Class Preferred Term	Primary System Organ Class Preferred Term
Subjects with at Least One Adverse Event	

As of 27 March 2013, there are 5 studies actively enrolling patients with multiple myeloma to investigate oral ixazomib in combination with standard combination regimens.

The most frequent (at least 10%) AEs occurring in the pooled safety population from Studies C16005, C16006, C16008, and C16013 are shown for all grades (Table 1-3). Note that in combination trials, related is defined as related to any study drug in the combination regimen.

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

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

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

Primary System Organ Class Preferred Term	Total Oral Combo Agent (5/6/8/13) n = 173 n (%)
Rash macular[a]	22 (13)
Musculoskeletal and connective tissue disorders	99 (57)
Back pain	42 (24)
Pain in extremity	31 (18)
Arthralgia	22 (13)
Respiratory, thoracic and mediastinal disorders	80 (46)
Cough	36 (21)
Dyspnoea	26 (15)
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 [6], non-Hodgkin's disease, Hodgkin's disease [7], relapsed and/or refractory multiple myeloma [RRMM; 8, 9], relapsed or refractory systemic light chain amyloidosis [RRAL; 10], and newly diagnosed multiple myeloma [NDMM; 11-13]) to date.

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

2.1.1.6 Relapsed and/or Refractory Multiple Myeloma

The early development of ixazomib in patients with RRMM involves 2 studies (C16003 and

C16004) with similar objectives, but each investigated 1 of the 2 dosing schedules commonly used with the first-in-class proteasome inhibitor, VELCADE.

Study C16003 is an open-label, dose escalation, phase 1 study of ixazomib dosing on a twice-weekly schedule on Days 1, 4, 8, and 11 of a 21-day cycle in adult patients with RRMM.(11, 12) Study C16004 is an open-label, dose escalation, phase 1 study of ixazomib dosing on a weekly schedule on Days 1, 8, and 15 of a 28-day cycle in adults patients with RRMM.(13, 14, 15) Both studies have now completed enrollment. The DLTs in Study C16003 were rash macular and thrombocytopenia and the DLTs in C16004 were nausea, diarrhea, vomiting, and erythema multiforme.

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

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

2.1.1.7 Newly Diagnosed Multiple Myeloma (NDMM)

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

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

2.1.1.8 Clinical Trial Experience Using the Intravenous Formulation of ixazomib

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

2.1.1.9 Potential Risks and Benefits

Please refer to the current ixazomib IB and SMA.

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

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

2.1.2 Rituximab

2.1.2.1 Description of Rituximab

Rituximab is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 cell surface antigen. The antibody is an IgG kappa immunoglobulin containing murine light- and heavy-chain variable region sequences and human constant region sequences. Rituximab is a composed of two heavy chains of 451 amino acids and two light chains of 213 amino acids (based on cDNA analysis) and has an approximate molecular weight of 145 kD. Rituximab has a binding affinity for the CD20 antigen of approximately 8.0 nM. The chimeric anti-CD20 antibody is produced by mammalian cell (Chinese Hamster ovary) suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product. Rituximab is purified by affinity and ion exchange chromatography. The purification process includes specific viral inactivation and removal procedures.

Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death has been reported in some patients with hematologic malignancies treated with rituximab. The majority of patients received rituximab in combination with chemotherapy. The median time to the diagnosis of hepatitis was approximately 4 months after the initiation of rituximab and approximately one month after the last dose.

2.1.2.2 Immunologic Events

Rituximab induced B-cell depletion occurred in 70 to 80% of patients, and was associated with decreased serum immunoglobulins in a minority of patients. The incidence of infection does not appear to be increased. During the treatment period, 50 patients in the pivotal trial developed 68 infectious events; 6 (9%) were grade 3 in severity, and none were Grade 4 events. Of the 6 serious infectious events, none were associated with neutropenia. The serious bacterial events included sepsis due to Listeria (n=1), staphylococcal bacteremia (n=1), and polymicrobial sepsis (n=1). In the post-treatment period (30 days to 11 months following the last dose), bacterial infections included sepsis (n=1); significant viral infections included herpes simplex infections (n=2) and herpes zoster (n=3). The following immune serious adverse events have been reported to occur rarely (<0.1%) in patients following completion of rituximab infusions: arthritis, disorders of blood vessels (vasculitis, serum sickness and lupus-like syndrome), lung disorders including pleuritis and scarring of the lung (bronchiolitis obliterans), eye disorders (uveitis and optic neuritis), and severe bullous skin reactions (including toxic epidermal necrolysis and pemphigus) that may result in fatal outcomes. Patients may have these symptoms alone or in combination with rash and polyarthritis.

Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death has been reported in some patients with hematologic malignancies treated with rituximab. The majority of patients received rituximab in combination with chemotherapy. The median time to the diagnosis of hepatitis was approximately 4 months after the initiation of rituximab and approximately one month after the last dose.

2.1.2.3 Retreatment Events

Twenty-one patients have received more than one course of Rituximab. The percentage of patients reporting any adverse event upon retreatment was similar to the percentage of patients reporting adverse events upon initial exposure. The following events were reported more frequently in retreated participants: asthenia, throat irritation, flushing, tachycardia, anorexia, leukopenia, thrombocytopenia, anemia, peripheral edema, dizziness, depression, respiratory symptoms, night sweats and pruritus.

2.1.2.4 Hematologic Events

In clinical trials, Grade 3 and 4 cytopenias were reported in 48% of patients treated with rituximab; these include: lymphopenia (40%), neutropenia (6%), leukopenia (4%), anemia (3%), and thrombocytopenia (2%). The median duration of lymphopenia was 14 days (range, 1 to 588 days) and of neutropenia was 13 days (range, 2 to 116 days). A single occurrence of transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following rituximab therapy were reported.

In addition, there have been a limited number of post marketing reports of prolonged pancytopenia, marrow hypoplasia, and late onset neutropenia (defined as occurring 40 days after the last dose of rituximab) in patients with hematologic malignancies. In reported cases of late onset neutropenia (NCI-CTC Grade 3 and 4), the median duration of neutropenia was 10 days (range 3 to 148 days). Documented resolution of the neutropenia was described in approximately one-half of the reported cases; of those with documented recovery, approximately half received

growth factor support. In the remaining cases, information on resolution was not provided. More than half of the reported cases of delayed onset neutropenia occurred in patients who had undergone prior autologous bone marrow transplantation. In an adequately designed, controlled, clinical trial, the reported incidence of NCI-CTC Grade 3 and 4 neutropenia was higher in patients receiving rituximab in combination with fludarabine as compared to those receiving fludarabine alone (76% [39/51] vs. 39% [21/53]).

2.1.2.5 Cardiopulmonary Events

Patients with pre-existing cardiac conditions, including arrhythmia and angina have had recurrences of these cardiac events during rituximab infusions. Four patients developed arrhythmias during rituximab infusion. One of the four discontinued treatment related incidence was because of ventricular tachycardia and supraventricular tachycardia. The other three patients experienced trigeminy (1) and irregular pulse (2) and did not require discontinuation of therapy. Angina was reported during infusion and myocardial infarction occurred 4 days post-infusion in one participant with a history of myocardial infarction. In rare cases, severe and fatal cardiopulmonary events, including hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, and cardiogenic shock have occurred. Nearly all-fatal infusion-related events occurred in association with the first infusion.

2.1.2.6 Potential for fatal infusion reactions

In post marketing studies, rare events of tumor lysis syndrome have been reported in patients who had a high number of circulating malignant cells (>25,000/ul), with a rapid reduction in tumor volume, renal insufficiency, hyperkalemia, hypocalcemia, hyperuricemia, and hyperphosphatemia noted in these patients. For additional details, and updates see current rituximab package insert. In rare cases, severe and fatal cardiopulmonary events, including hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, and cardiogenic shock, have occurred. Nearly all-fatal infusion-related events occurred in association with the first infusion.

2.1.2.7 Prevention and management of abrupt increases in serum IgM and viscosity following Rituximab use in patents with WM.

Abrupt and paradoxical increases in IgM levels have been reported with the use of rituximab in patients with WM, which may aggravate hyperviscosity and contribute to hyperviscosity related symptoms. Plasmapheresis is strongly encouraged for those patients at increased risk for hyperviscosity. Rituximab will also be omitted for Cycles 1and/or 2 as necessary and at the discretion of the Principal Investigator for at risk patients.

2.1.3 Dexamethasone

2.1.3.1 Intravenous Dexamethasone

Each mL of clear, colorless sterile solution contains: dexamethasone sodium phosphate equivalent to dexamethasone phosphate 4 mg (equal to 3.33 mg of dexamethasone or roughly

about 100 mg of hydrocortisone). Non-medicinal ingredients: creatinine, sodium citrate, sodium hydroxide (to adjust pH) and water for injection with sodium bisulfite, methylparaben, and propylparaben are added as preservatives.

2.1.3.2 Oral Dexamethasone

Dexamethasone is commercially available as tablets for oral administration in following potencies: 0.25 mg, 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 4 mg, and 6 mg. Inactive ingredients are calcium phosphate, lactose, magnesium stearate, and starch.

In the unlikely event of a drug supply interruption, oral dexamethasone will be substituted for IV dexamethasone at same dose used for intravenous administration.

2.1.3.3 Contraindications for Dexamethasone therapy

Dexamethasone will be omitted from therapy while on study in the following circumstances:

- History of tuberculosis or other granulomatous disease;
- Systemic fungal infection;
- History of or development of uncontrollable steroid related glucose intolerance;
- History of or development of steroid related hypersensitivity;
- Intolerance due to gastric and duodenal ulcers despite adequate upper gastrointestinal prophylactic therapy.
- Recipient of a live virus vaccine within 30 days.
- Pregnancy and lactation.
- Development of moderate to severe acute infections.

In the event dexamethasone is omitted, patients will not be removed from study treatment, and will continue to receive all other intended therapy on study.

2.1.3.4 Drug-Interactions for Dexamethasone

The following drug interactions with dexamethasone have been reported:

- Concurrent administration of dexamethasone with thiazides or furosemide may cause excessive potassium loss.
- Dexamethasone may decrease the effect of anti-muscarinic drugs.
- Dexamethasone may increase the incidence of gastro-intestinal ulceration when administered concurrently with non-steroidal anti-inflammatory drugs.
- Barbiturates, phenytoin, rifampicin, ephedrine, may enhance the metabolism clearance of corticosteroids and reduce the effects of dexamethasone.
- Dexamethasone decreases the serum concentration of salicylates.
- Response to anticoagulants may be altered by dexamethasone.

2.1.3.5 Adverse Events with Dexamethasone

Fluid and electrolyte disturbances: sodium retention; fluid retention; congestive heart failure in susceptible patients; potassium loss; hypokalemic alkalosis; hypertension; hypotension or shock-like reaction.

Musculoskeletal: muscle weakness; steroid myopathy; loss of muscle mass; osteoporosis; vertebral compression fractures; aseptic necrosis of femoral and humeral heads; pathologic fracture of long bones; tendon rupture.

Gastrointestinal: peptic ulcer with possible subsequent perforation and hemorrhage; perforation of the small and large bowel, particularly in patients with inflammatory bowel disease; pancreatitis; abdominal distention; ulcerative esophagitis.

Dermatologic: impaired wound healing; thin fragile skin; petechiae and ecchymoses; erythema; increased sweating; may suppress reactions to skin tests, burning or tingling, especially in the perineal area (after i.v. injection), other cutaneous reactions such as allergic dermatitis, urticaria, angioneurotic edema.

Neurological: convulsions; increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment; vertigo; headache; psychic disturbances.

Endocrine: menstrual irregularities; development of cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetes; hirsutism.

Ophthalmic: posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos; retinopathy of prematurity.

Cardiovascular: myocardial rupture following recent myocardial infarction; hypertrophic cardiomyopathy in low birth weight infants.

Metabolic: negative nitrogen balance due to protein catabolism.

Other: anaphylactoid or hypersensitivity reactions, thromboembolism, weight gain, increased appetite, nausea, malaise, hiccups.

The following additional adverse reactions are related to parenteral corticosteroid therapy: rare instances of blindness associated with intralesional therapy around the face and head; hyperpigmentation or hypopigmentation; s.c. and cutaneous atrophy; sterile abscess; post injection flare (following intra-articular use); Charcot-like arthropathy.

2.2Study Disease

WM is a rare B-cell lymphoproliferative disorder characterized by the uncontrolled accumulation of IgM-producing lymphoplasmacytic cells. The disease was first reported by Jan Waldenström,

who described two patients with a high level of macroglobulin, i.e. pentameric immunoglobulin M (IgM), marked hyperviscosity, typical funduscopic picture and lymphocytoid bone marrow infiltration (Waldenström 1944). Such malignant cells accumulate in the bone marrow, liver, spleen and lymph nodes. WM is diagnosed by the presence of lymphoplasmacytic cells in the bone marrow and an IgM monoclonal spike (M-spike) identified in a serum protein electrophoresis (SPEP) (Owen 2003). The incidence of WM in the United States (US) is approximately 3 per million persons per year accounting for 1000-1500 new cases per year. The clinical course of WM is variable and although patients might experience an overall survival (OS) measured in decades, WM remains incurable with current therapeutic regimens. Hence, the disease course is characterized by continual relapses, each harder to treat than the previous one. Additionally, many of the disabling symptoms associated with the disease, such as hyperviscosity, fatigue, anemia and/or neuropathy, can be exacerbated by our therapy. Hence, the careful evaluation of agents with novel mechanisms of action is needed to improve the quality of life (QOL), and response and survival rates in patients with WM.

2.3Rationale

Despite advances in the treatment, WM remains incurable and as such; novel therapeutics are needed. Among the first line treatment options for WM are oral alkylators such as chlorambucil, nucleoside analogues, rituximab, alone and in combination treatment, thalidomide, and bortezomib (Treon 2006; Dimopoulos 2008). The use of oral alkylators and nucleoside analogues is associated with risk of myelodysplasia/acute leukemia, disease transformation and stem cell damage thereby limiting their usefulness, particularly in younger stem cell eligible transplant patients (Treon 2009a; Leleu 2009). Rituximab is an important therapeutic, generating overall response rates in 30-40% of patients. Among WM patients receiving rituximab as monotherapy, lower response rates have been observed in those patients with high serum IgM (>6,000 mg/dL) and beta-2 microglobulin (B2M) (>3.0 mg/L) levels, as well as homozygous expression of phenylalanine at amino acid position 158 on CD16 (FcγRIIIA-158) (Treon 2005a; Dimopoulos 2005; Treon 2005b). Limiting the application of rituximab is an idiopathic IgM flare phenomenon, which can provoke symptomatic hyperviscosity, as well as symptomatic IgM related morbidity. Moreover, patients with WM appear to develop earlier intolerance to rituximab versus patients with other indolent lymphomas, which may be related to the frequent presence of auto-IgG antibodies in WM patients.

Bortezomib (Velcade®) is active in WM. As a single agent in relapsed/refractory WM, overall response rates of 40-60% have been reported. In combination with rituximab, higher response rates have been observed in relapsed/refractory or untreated patients (70-80%). The combination of bortezomib with dexamethasone and rituximab (BDR) is particularly active as primary therapy in WM with 96% overall response rate, and VGPR or better categorical responses in 35% of patients. In a recent update at the 6th International Workshop on WM, the projected progression free survival for BDR was estimated at >56 months. An important limitation however to the use of bortezomib is the development of ≥grade 3 peripheral neuropathy in 20-30% of patients using twice a week schedule of administration, and 5-10% with once a week. However, CR rates are potentially lower (5% vs. 20%), and risk of rituximab related IgM flare higher (20% vs. 10%) with attenuation of bortezomib dose to once a week, versus twice a week.

(Treon 2009b; Ghobrial 2010). As such, the identification of novel, neuropathy and stem cell sparing agents is an important goal for therapy of WM.

We recently reported our experience with the combination of carfilzomib (Kyprolis®), dexamethasone and rituximab (CaRD) in 31 proteasome-inhibitor- and rituximab-naïve patients with WM (Treon 2013). Carfilzomib was administered IV on days 1, 2, 8 and 9 every 3 weeks. The median IgM levels declined from 3,510 mg/dL to 1,876 mg/dL, and the median M-protein from 2.09 g/dL to 0.99 g/dL. Median hemoglobin levels improved from 10.6 g/dL to 12 g/dL. Bone marrow tumor burden decreased from a median of 60% to 10%. The ORR was 74% (1 CR, 6 VGPR, 9 PR and 1 MR). The treatment was well tolerated with the only grade 3 or 4 AE of neutropenia (7%). Grade 1 peripheral neuropathy developed in 19% of the patients. There was no grade 2 or higher peripheral neuropathy.

2.4 Correlative Studies Background

2.4.1 MYD88 L265P and CXCR4-WHIM-like mutations, and FcγRIIIA-158 (CD16) polymorphisms

One of the major advances in the field of WM has been the recent discovery of a recurrent genetic abnormality, the MYD88 L265P mutation (Treon 2012). Sanger sequencing detected such mutation in tumor samples from 49 out of 54 patients (91%) with WM. Interestingly, the mutation was not detected in normal cells from WM patients and B-cells from healthy donors, and was absent or rarely expressed in cells from patients with multiple myeloma or marginal zone lymphoma. Such finding has been independently validated in subsequent studies from Italy, France the United States with prevalence rates ranging between 90-100% (Varettoni 2013; Poulain 2013; Ondrejka 2013). More recently, allele-specific PCR assays have been developed to improve the sensitivity of detection of the mutation and the quantification of the MYD88 L265P mutation burden (Xu 2013).

More recently, mutations in the CXC chemokine receptor 4 (CXCR4) gene were identified in 16 out of 55 (29%) WM patients investigated (Cao 2012). CXCR4 mutations are the second most common mutations found in WM patients. Such mutations are similar to the ones seen in patients with WHIM syndrome, an autosomal dominant genetic disorder characterized by warts, hypogammaglobulinemia, infections and myelokathexis (Hunter 2013) conferring gain of function and decreased CXCR4 internalization. In preclinical and clinical studies, CXCR4-WHIM mutations have been associated with lower responses to Bruton tyrosine kinase inhibitors (Cao 2013), but their significance in proteasome inhibitor-treated patients is not yet known.

As part of these efforts, the impact of FcγRIIIA-158 (CD16) polymorphisms as a predictor of categorical response in WM will be assessed. In previous studies by Treon et al, the presence of at least one valine at amino acid position 158 at FcγRIIIA (CD16) predicted for response to rituximab (Treon 2005b). Patients displaying either valine/valine (V/V) or valine/phenylalanine (V/F) had a four-fold higher rate of response to single agent rituximab compared to patients displaying phenylalanine/phenylalanine (F/F) alone at FcγRIIIA-158. The impact of polymorphisms at FcγRIIIA-158 on response outcome has also been validated in other indolent

lymphomas (Cartron 2002; Weng 2003), and has lead to U.S. FDA clearance for such testing. The impact of FcγRIIIA-158 polymorphisms in predicting categorical response attainment in WM patients has recently been reported. Hunter et al demonstrated that better categorical responses (i.e. VGPR or better) were associated with V/V or V/F at FcγRIIIA-158 in patients who received combination therapy with rituximab (Treon 2011). As such, as part of these studies we will seek to determine the impact of FcγRIIIA-158 polymorphisms on categorical response attainment in WM patients in this study.

3.PARTICIPANT SELECTION

3.1Eligibility Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

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

1. Male or female patients 18 years or older.
2. Voluntary written consent must be given before performance of any study related procedure not part of standard medical care, with the understanding that the patient may withdraw consent at any time without prejudice to future medical care.
3. Female patients who:
   - Are postmenopausal for at least 1 year before the screening visit, OR
   - Are surgically sterile, OR
   - Are of childbearing potential,
     - agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through 90 days after the last dose of study drug, OR
     - Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

   Male patients, even if surgically sterilized (ie, status post-vasectomy), must agree to one of the following:
   - Agree to practice effective barrier contraception during the entire study treatment period and through *90 days* after the last dose of study drug, OR
   - Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)
4. Patients must have a clinicopathological diagnosis of WM (Owen 2003), with symptomatic disease meeting criteria for treatment using consensus panel criteria from the Second International Workshop on WM (Kyle 2003) or serum IgM >6000 mg/dL, and measurable disease, defined as presence of immunoglobulin M (IgM) paraprotein with a minimum IgM level of >2 times the upper limit of normal.
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.

6. Patients must meet the following clinical laboratory criteria
7. Absolute neutrophil count (ANC) ≥1,000/mm^3 and platelet count ≥75,000/mm^3. Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days before study enrollment.
8. Total bilirubin ≤1.5 × the upper limit of the normal range (ULN).
9. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 × ULN.
10. Calculated creatinine clearance ≥ 30 mL/min.

3.2Exclusion Criteria

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

1. Female patients who are lactating or have a positive serum pregnancy test during the screening period.
2. Major surgery within 14 days before enrollment.
3. Central nervous system involvement.
4. Infection requiring systemic antibiotic therapy or other serious infection within 14 days before study enrollment.
5. 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.
6. Systemic treatment, within 14 days before the first dose of MLN9708, 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.
7. Known hepatitis B or C virus, or human immunodeficiency virus (HIV) infection.
8. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
9. Known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent.
10. Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of ixazomib including difficulty swallowing.
11. 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. Male patients with incidental histological findings of prostate cancer (T1a or T1b using the TNM (tumor nodes, metastasis) clinical staging system are not excluded.
12. Participation in other clinical trials, including those with other investigational agents not included in this trial, within 30 days of the start of this trial and throughout the duration of this trial.

4.REGISTRATION PROCEDURES

4.1General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registration must occur prior to the initiation of therapy. Any participant not registered to the protocol before treatment begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol treatment. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

4.2Registration Process for DF/HCC and DF/PCC Institutions

5.TREATMENT PLAN

Treatment will be administered on an outpatient or inpatient basis. Expected toxicities and potential risks as well as dose modifications for ixazomib, rituximab, and dexamethasone are described in Section 6 (Expected Toxicities and Dosing Delays/Dose Modification). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

IDR Induction Phase					
Agent	**Premedications**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Dexamethasone	None	20 mg	IV or PO	Days 1, 8, 15 Before ixazomib and rituximab	Every 4 weeks for Cycles 1-6 Rituximab omitted from cycles 1 and 2
Ixazomib	None	4 mg	PO	Days 1, 8 15 After dexamethasone	
Rituximab	Diphenhydramine 25-50 mg PO/IV Acetaminophen 650-1000 mg PO Famotidine 20mg IV	375 mg/m^2	IV infusion	Day 1 After Ixazomib	

IDR Maintenance Phase					
Agent	**Premedications**	**Dose**	**Route**	**Schedule**	**Cycle Length**

Dexamethasone	None	20 mg	IV or PO	Day 1, 8, and 15 Before Ixazomib and Rituximab	Every 8 weeks +/- 2 weeks for Cycles 1-6
Ixazomib	None	4 mg	PO	Day 1, 8, and 15 After Dexamethasone	
Rituximab	Diphenhydramine 25-50 mg PO/IV Acetaminophen 650-1000 mg PO Famotidine 20mg IV	375 mg/m^2	IV infusion	Day 1 After Ixazomib	

5.1 Pre-Medication

5.1.1 Rituximab

To prevent infusion related or hypersensitivity reactions from occurring during infusion of rituximab, premedication consisting of diphenhydramine 25-50 mg PO/IV, and Acetaminophen 650-1000 mg PO should be given to patients prior to administration of all infusions of rituximab, unless the patient has an allergy to either medication. Since transient hypotension may occur during rituximab administration, consideration should be given to withholding anti-hypertensive medications 12 hours prior to rituximab infusion. Prophylactic anti-emetic therapy for rituximab is generally not necessary, but may used at the discretion of the treating physician.

5.2 Agent Administration

5.2.1 Ixazomib

5.2.1.1 Form of Ixazomib

All later phase studies are conducted with the Capsule formulation.

Ixazomib Capsules

The ixazomib drug product is provided in strengths of 4.0-, 3.0-, and 2.3-mg and 2.0-, 0.5-, and 0.2 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
2.0 mg	Size 2	Swedish orange
0.5 mg	Size 3	Dark green
0.2 mg	Size 4	White opaque

Ixazomib Capsules are individually packaged in foil-foil blisters with a paper backing for child resistance.

For additional details, please see the ixazomib IB.

5.2.1.2 Hydration

IV hydration is recommended prior to ixazomib for Cycle 1 of induction therapy ONLY. This will consist of 500 mL normal saline or other appropriate IV fluid over 1 hour. IV hydration in subsequent cycles will be at the discretion of the Principal Investigator.

5.2.1.3 Ixazomib Administration

Ixazomib should be administered after dexamethasone each and every cycle, unless dexamethasone is omitted. Please refer to section 2.1.3.3. The order of administration should be dexamethasone followed by ixazomib followed by rituximab.

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 6.2).

Capsules of **ixazomib** will also be referred to as study drug. Study drug will be supplied by Millennium as capsules of 2.3, 3.0 and 4.0 mg **ixazomib**. The prescribed administration of **ixazomib** doses in this study is 4 mg **ixazomib** PO once weekly (+/-3 days) on days 1, 8 and 15 in a 28-day cycle during induction therapy, and once on days 1, 8, and 15 in each maintenance cycle.

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

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

Ixazomib drug product is an anti-cancer drug. Refer to the published institutional guidelines regarding the proper handling and disposal of anti-cancer agents.

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

accountability logs.

5.2.2 Rituximab

5.2.2.1 Form of Rituximab

Rituximab is supplied as a sterile, colorless, preservative free liquid concentrate for intravenous (IV) administration. Rituximab is supplied at a concentration of 10 mg/ml in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials. The product is formulated for IV administration in 9 mg/ml sodium chloride, 7.35-mg/mL sodium citrate dehydrate, 0.7 mg/mL polysorbate 80, and sterile water for injection. The pH is adjusted to 6.5.

5.2.2.2 Method of Procurement for Rituximab

Rituximab is a commercially available drug, which is approved by the U.S. Food and Drug Administration for use in patients with low grade and follicular Non-Hodgkin Lymphoma (NHL). Use of this drug to treat patients with lymphoplasmacytic lymphoma (Waldenstrom's macroglobulinemia) is considered to be a labeled indication since it is included under the indolent NHL indication. Drug used in this study will be billed to patient and/or their third party payer (insurance).

5.2.2.3 Drug Stability and Compatibility of Rituximab

Rituximab vials are stable at 2°-8° C. Vials of rituximab beyond expiration date on the carton should not be used. Rituximab vials should be protected from direct sunlight.

5.2.2.4 Preparation of Rituximab

Rituximab is diluted to a final concentration of 1 to 4 mg/ml into an infusion bag containing either 0.9% sodium chloride USP or 5% dextrose in water USP. Rituximab solutions for infusion are stable at 2° to 8° C for 24 hours and at room temperature for an additional 12 hours. No incompatibilities between rituximab and polyvinylchloride or polyethylene bags have been reported.

5.2.2.5 Rituximab Pre-Treatment Medications

To prevent infusion related or hypersensitivity reactions from occurring during infusion of rituximab, premedication consisting of diphenhydramine 25-50 mg IV, and acetaminophen 650-1000 mg PO should be given to patients prior to administration of all infusions of rituximab, unless the patient has an allergy to either medication. Lower doses may be used if the patient demonstrates tolerance. Since transient hypotension may occur during rituximab administration, consideration should be given to withholding anti-hypertensive medications 12 hours prior to rituximab infusion. Prophylactic anti-emetic therapy for rituximab is generally not necessary, but may used at the discretion of the treating physician.

5.2.2.6 Rituximab Treatment Schedule and Administration

Rituximab should be administered after ixazomib on day 1 of induction cycles 3-6 and maintenance cycles 1-6. The order of administration should be dexamethasone followed by ixazomib followed by rituximab. Please see section 5.2.1.3.

During the induction phase Cycles 3-6 on Day 1 and the maintenance phase Cycles 1-6 on Day 1, Rituximab 375 mg/m^2 IV is to be administered at an initial rate of 50 mg/hour for the first hour then escalate the rate in 50 mg/ hours increments approximately every 30 minutes, to a maximum of 400 mg/hour. If hypersensitivity or an infusion-related event develops such as T>101.3, mucosal edema, or a >30mm Hg decrease in SBP, interrupt the infusion, administer hypersensitivity rescue medications. When symptoms have resolved, the infusion can continue at one-half the previous rate and escalate in 50 mg/hr increments approximately each half hour, as tolerated. The infusion may be discontinued early at the discretion of the treating investigator. For patients who have tolerated previous infusions without hypersensitivity, subsequent infusions can be administered at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at approximately 30-minute intervals, to a maximum of 400 mg/hr as tolerated. Alternatively, subsequent infusions can be administered at an initial rate of 20 percent of the total dose over 30 minutes, followed by the remaining 80 percent of the total dose over 60 minutes.

Vital signs: At the first infusion, vital signs should be checked and recorded at baseline, at the first rate change (usually at the approximately 1 hour point), as needed for signs and symptoms of hypersensitivity reaction, and at the end of the infusion. For subsequent infusions, vitals should be taken at baseline, and as needed for signs or symptoms of a reaction.

5.2.2.7 First Infusion of Rituximab

The rituximab solution for infusion should be administered intravenously at an initial rate of 50 mg/hr. Rituximab should not be mixed or diluted with other drugs. If hypersensitivity or infusion related events do not occur, the infusion can be escalated in 50 mg/hr increments approximately every 30 minutes, to a maximum of 400 mg/hr. If hypersensitivity or an infusion-related event develops, such as, T>101.3, mucosal edema, or a >30mm Hg decrease in SBP interrupt the infusion, administer hypersensitivity rescue medications. When symptoms have resolved, the infusion can continue at one-half the previous rate and escalate in 50 mg/hr increments each half hour, as tolerated.

5.2.2.8 Subsequent Rituximab infusions

Subsequent rituximab infusions can be administered at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at approximately 30-minute intervals, to a maximum of 400 mg/hr as tolerated. Rituximab is administered intravenously. Alternatively, subsequent infusions can be administered at an initial rate of 20 percent of the total dose over 30 minutes, followed by the remaining 80 percent of the total dose over 60 minutes. To prevent infusion related or hypersensitivity events, **Rituximab is not to be administered as an intravenous push or bolus.**

5.2.2.9 Modification of Rate for Infusion of Rituximab

In the event that patients develop an infusion related or hypersensitivity reaction to rituximab then the rate of drug administration is altered as described above. The total dose administered remains the same in such cases. In the event of serious or life threatening reactions, the infusion should be terminated and such adverse events reported. In the event of serious or life threatening events attributed to rituximab, patients may permanently discontinue rituximab and remain on the study after consultation with the overall PI.

5.2.3 Dexamethasone

5.2.3.1 Intravenous Dexamethasone

Each mL of clear, colorless sterile solution contains: dexamethasone sodium phosphate equivalent to dexamethasone phosphate 4 mg (equal to 3.33 mg of dexamethasone or roughly about 100 mg of hydrocortisone). Non-medicinal ingredients: creatinine, sodium citrate, sodium hydroxide (to adjust pH) and water for injection with sodium bisulfite, methylparaben, and propylparaben are added as preservatives. Store below 25°C. Do not freeze. Protect from light.

5.2.3.2 Contraindications and Drug interactions for Dexamethasone therapy

Refer to sections 2.1.3.3 and 2.1.3.4 for contra-indications and drug interactions with dexamethasone.

5.2.3.3 Dexamethasone Administration

Dexamethasone should be administered before ixazomib unless dexamethasone is omitted. Please refer to section 2.3.3.3. The order of administration should be dexamethasone followed by ixazomib followed by rituximab. Please see section 5.2.1.3.

During the induction phase, Cycles 1-6, Days 1, 8 and 15, a total of 20 mg IV or PO dexamethasone will be administered before ixazomib. During the maintenance phase, Cycles 1-8, Day 1, a total of 20 mg IV or PO dexamethasone will be administered.

20 mg oral dexamethasone may be substituted in the event of a drug supply shortage of IV dexamethasone and on days 8 and 15 of induction and maintenance for dosing outside of clinic. Administration method will be documented.

5.3General Concomitant Medication and Supportive Care Guidelines

Concomitant medication is defined as any prescription or over-the-counter preparation including vitamins and supplements. All required and optional/allowed concomitant medications must be recorded from screening through the end of the participant's study participation. Any change in concomitant medications must be recorded.

5.3.1 Required Concomitant Medications

Female participants of childbearing potential must agree to use methods of contraception for the duration of the study. Male participants must agree to use a barrier method of contraception for the duration of the study if sexually active with a female of childbearing potential. Surgically sterilized patients are except from contraception requirements.

All participants will receive 400 mg orally twice daily of acyclovir or valcyclovir 1000 mg orally daily, unless contraindicated, for Herpes zoster prophylaxis for the duration of the trial and for at least 6 months following completion of ixazomib treatment.

5.3.2 Optional and Allowed Concomitant Medications

Supportive care is permitted as medically needed. Participants may receive supportive care with erythropoietin, darbepoetin, filgrastim or pegfilgrastim, in accordance with institutional guidelines.

Participants may receive RBC or platelet transfusions if clinically indicated in accordance with institutional guidelines. Participants who require repeated platelet transfusion support should be discussed with the principal investigator.

Participants may receive antiemetic and antidiarrheal medications as necessary, but these should not be administered unless indicated. Colony-stimulating factors may be used if neutropenia occurs but should not be given prophylactically.

All vitamins and supplements must be recorded from screening through the end of the participant's participation on trial.

Green tea and/or green tea supplements are prohibited while participating on trial.

5.4Duration of Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse events, treatment may continue for 6 cycles of induction therapy with 6 cycles of maintenance or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Participant demonstrates an inability or unwillingness to comply with the regimen and/or documentation requirements
- Participant decides to withdraw from the study, or
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.

5.5Duration of Follow Up

Participants will be followed every six months (every 3 months preferred) for two years after removal from study until next therapy or until death. Participants removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

5.6Criteria for Removal from Study

Participants will be removed from study when any of the criteria listed in Section 5.4 applies. The reason for study removal and the date the participant was removed must be documented in the study-specific case report form (CRF). Alternative care options will be discussed with the participant.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator, **Dr. Jorge J. Castillo, Phone: 401-489-4626.**

6.EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made using these recommendations. Toxicity assessments will be done using the CTEP Version 4 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0, which is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including antiemetic, antidiarrheal agents, etc.).

All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the final study visit. Participants continuing to experience toxicity at the off study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

6.1Anticipated toxicities

6.1.1Adverse Event Lists for Ixazomib

Table 6-1 Most frequent treatment-emergent adverse events (in at least 10% of patients), overall safety population (part 1)

Primary System Organ Class Preferred Term	IV Total n = 146 n (%)	Oral Single Agent (3/4/7/9) n = 201 n (%)	Oral Combo (5/6/8/13) n = 173 n (%)	Oral Total n = 384 n (%)	Overall Total N = 530 n (%)
Subjects with at Least One Adverse Event	145 (99)	197 (98)	163 (94)	370 (96)	515 (97)
Gastrointestinal disorders	115 (79)	160 (80)	139 (80)	306 (80)	421 (79)
Nausea	59 (40)	106 (53)	65 (38)	175 (46)	234 (44)
Diarrhoea	49 (34)	88 (44)	81 (47)	175 (46)	224 (42)
Vomiting	59 (40)	77 (38)	51 (29)	132 (34)	191 (36)
Constipation	36 (25)	46 (23)	57 (33)	105 (27)	141 (27)
Abdominal pain	27 (18)	33 (16)	14 (8)	49 (13)	76 (14)
General disorders and administration site conditions	118 (81)	151 (75)	132 (76)	288 (75)	406 (77)
Fatigue	88 (60)	103 (51)	76 (44)	181 (47)	269 (51)
Pyrexia	45 (31)	51 (25)	39 (23)	93 (24)	138 (26)
Oedema peripheral	30 (21)	27 (13)	61 (35)	89 (23)	119 (22)
Asthenia	10 (7)	31 (15)	20 (12)	51 (13)	61 (12)
Nervous system disorders	86 (59)	92 (46)	115 (66)	210 (55)	296 (56)
Headache	31 (21)	29 (14)	28 (16)	58 (15)	89 (17)
Dizziness	25 (17)	26 (13)	34 (20)	60 (16)	85 (16)
Neuropathy peripheral	16 (11)	21 (10)	45 (26)	66 (17)	82 (15)
Metabolism and nutrition disorders	88 (60)	107 (53)	91 (53)	204 (53)	292 (55)
Decreased appetite	55 (38)	64 (32)	25 (14)	92 (24)	147 (28)
Dehydration	25 (17)	37 (18)	12 (7)	49 (13)	74 (14)
Hypokalaemia	10 (7)	11 (5)	34 (20)	47 (12)	57 (11)
Blood and lymphatic system disorders	88 (60)	98 (49)	88 (51)	195 (51)	283 (53)
Thrombocytopenia	65 (45)	68 (34)	49 (28)	124 (32)	189 (36)
Anaemia	28 (19)	42 (21)	45 (26)	89 (23)	117 (22)

Table 6-1 Most frequent treatment-emergent adverse events (in at least 10% of patients), overall safety population (part 2)

Primary System Organ Class Preferred Term	IV Total n = 146 n (%)	Oral Single Agent (3/4/7/9) n = 201 n (%)	Oral Combo (5/6/8/13) n = 173 n (%)	Oral Total n = 384 n (%)	Overall Total N = 530 n (%)
Neutropenia	16 (11)	29 (14)	43 (25)	79 (21)	95 (18)
Lymphopenia	16 (11)	20 (10)	20 (12)	47 (12)	63 (12)
Skin and subcutaneous tissue disorders	83 (57)	90 (45)	102 (59)	195 (51)	278 (52)
Rash maculo-papular	21 (14)	13 (6)	29 (17)	44 (11)	65 (12)
Musculoskeletal and connective tissue disorders	78 (53)	93 (46)	99 (57)	193 (50)	271 (51)
Back pain	27 (18)	24 (12)	42 (24)	66 (17)	93 (18)
Pain in extremity	21 (14)	18 (9)	31 (18)	49 (13)	70 (13)
Arthralgia	17 (12)	28 (14)	22 (13)	50 (13)	67 (13)
Respiratory, thoracic and mediastinal disorders	87 (60)	78 (39)	80 (46)	161 (42)	248 (47)
Cough	31 (21)	28 (14)	36 (21)	64 (17)	95 (18)
Dyspnoea	30 (21)	30 (15)	26 (15)	56 (15)	86 (16)
Infections and infestations	48 (33)	89 (44)	92 (53)	184 (48)	232 (44)
Upper respiratory tract infection	12 (8)	31 (15)	35 (20)	66 (17)	78 (15)
Psychiatric disorders	32 (22)	35 (17)	73 (42)	113 (29)	145 (27)
Insomnia	14 (10)	12 (6)	50 (29)	67 (17)	81 (15)

Source: \biostatistics\MLNM9708\IB\2013\Tables\T14.1.3-TEAE_Pct10_Pooled 04APR2013 10:48

Table 6-2 Treatment-emergent rash events, overall safety population (part 1)

MedDRA High-Level Term Preferred Term	IV (C16001/2) n = 146 n (%)	Oral Single Agent (C16003/4/7/9) n = 201 n (%)	Oral Combo Agent (C16005/6/8/13) n = 173 n (%)	Oral Total n = 384 n (%)	Overall Tota N = 530 n (%)
Rashes, eruptions and exanthems NEC	41 (28)	40 (20)	54 (31)	96 (25)	137 (26)
Rash maculo-papular	21 (14)	13 (6)	29 (17)	44 (11)	65 (12)
Rash macular	15 (10)	23 (11)	22 (13)	45 (12)	60 (11)
Rash	10 (7)	8 (4)	12 (7)	20 (5)	30 (6)
Rash generalised	0	1 (< 1)	1 (< 1)	2 (< 1)	2 (< 1)
Rash vesicular	0	1 (< 1)	1 (< 1)	2 (< 1)	2 (< 1)
Rash morbilliform	0	1 (< 1)	0	1 (< 1)	1 (< 1)
Pruritus NEC	29 (20)	21 (10)	28 (16)	49 (13)	78 (15)
Rash pruritic	20 (14)	9 (4)	16 (9)	25 (7)	45 (8)
Pruritus	12 (8)	13 (6)	14 (8)	27 (7)	39 (7)
Pruritus generalised	0	0	1 (< 1)	1 (< 1)	1 (< 1)
Erythemas	15 (10)	9 (4)	15 (9)	24 (6)	39 (7)
Rash erythematous	12 (8)	3 (1)	8 (5)	11 (3)	23 (4)
Erythema	3 (2)	6 (3)	7 (4)	13 (3)	16 (3)
Palmar erythema	0	0	1 (< 1)	1 (< 1)	1 (< 1)
Papulosquamous conditions	13 (9)	8 (4)	7 (4)	15 (4)	28 (5)
Rash papular	13 (9)	8 (4)	7 (4)	15 (4)	28 (5)
Exfoliative conditions	4 (3)	8 (4)	4 (2)	12 (3)	16 (3)
Skin exfoliation	2 (1)	5 (2)	2 (1)	7 (2)	9 (2)
Exfoliative rash	2 (1)	2 (< 1)	0	2 (< 1)	4 (< 1)
Dermatitis exfoliative	0	1 (< 1)	2 (1)	3 (< 1)	3 (< 1)
Acute febrile neutrophilic dermatosis	0	2 (< 1)	1 (< 1)	3 (< 1)	3 (< 1)
Dermatitis allergic	0	0	3 (2)	3 (< 1)	3 (< 1)
Dermatitis acneiform	4 (3)	1 (< 1)	3 (2)	4 (1)	7 (1)
Erythema multiforme	0	2 (< 1)	1 (< 1)	3 (< 1)	3 (< 1)

Table 6-2 Treatment-emergent rash events, overall safety population (part 2)

MedDRA High-Level Term Preferred Term	IV (C16001/2) n = 146 n (%)	Oral Single Agent (C16003/4/7/9) n = 201 n (%)	Oral Combo Agent (C16005/6/8/13) n = 173 n (%)	Oral Total n = 384 n (%)	Overall Total N = 530 n (%)
Stevens-Johnson syndrome	0	1 (< 1)	1 (< 1)	2 (< 1)	2 (< 1)
Interstitial granulomatous dermatitis	0	1 (< 1)	0	0	1 (< 1)
Vasculitic rash	0	1 (< 1)	0	1 (< 1)	1 (< 1)

Source: \\biostatistics\MLNM9708\IB\2013\Tables\T14.6.1-TEAE_AESI_Pooled;
\\biostatistics\MLNM9708\IB\2013\Tables\T14.1.2-TEAE_All 05APR2013 12:20.

6.1.2 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

- Systemic treatment with any of the following metabolizing enzyme inhibitors is not permitted during this study. **A drug-drug interaction [DDI] with a strong inhibitor would increase the ixazomib exposure and could lead to a higher probability of an AE).** Strong inhibitors of CYP1A2: fluvoxamine, enoxacin, ciprofloxacin.
- Strong inhibitors of CYP3A: clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, and posaconazole. Systemic treatment with any of the following metabolizing enzyme inducers should be avoided unless there is no appropriate alternative medication for the patient's use. **Unlike with inhibitors, if there were to be a DDI with an inducer, ixazomib exposure would be less; therefore, there would be a reduced chance of an AE. However, there may be less chance for an antitumor effect, but that is not an absolute reason to be taken off ixazomib.**
- Strong CYP3A inducers: rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, and phenobarbital
- The dietary supplements St John's wort and Ginkgo biloba are not permitted.

The following procedures are prohibited during the study:

- Any antineoplastic treatment with activity against WM (i.e. high-dose steroids, methotrexate, cyclophosphamide, etc.) except for drugs in this treatment regimen.
- Radiation therapy **(note that, in general, the requirement for local radiation therapy indicates disease progression)**
- **Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days prior to the blood draw that will confirm eligibility or any pre-dose CBC blood draws to guide dosing decisions (see Section 6.2.1.1)**

6.1.3 Permitted Concomitant Medications and Procedures ***(if applicable)***

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;. Erythropoietin will be allowed in this study. Their use should follow published guidelines and/or institutional practice.
- **Patients should be transfused with red cells and platelets as clinically indicated and according to institutional guidelines.** Patients should not have a CBC drawn to confirm eligibility or for on-treatment decisions (see section 6.2.1.1: Dose Reductions for Hematologic Toxicities) less than 3 days following a platelet transfusion. Patients MUST HAVE a CBC drawn to confirm eligibility or for on-treatment decisions (see section 6.2.1.1: Dose Reductions for Hematologic Toxicities) more than 3 days following a platelet transfusion. If a patient receives a platelet transfusion, then a 3-day wait is recommended for the CBC draw that would either confirm eligibility or guide the decision with regards to the next dose (drug hold/dose reduce per Section 6.2.1.1).
- Antiviral therapy such as acyclovir may be administered if medically appropriate.
- Concomitant treatment with bisphosphonates will be permitted, as appropriate.
- Patients who experience worsening neuropathy from baseline may be observed for recovery, and have dose reductions/delays as indicated in the protocol, and any supportive therapy or intervention may be initiated as appropriate at the discretion of the investigator.
- Supportive measures consistent with optimal patient care may be given throughout the study.

6.1.4 Precautions and Restrictions

- **Fluid deficit should be corrected before initiation of treatment and during treatment.**

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided with impaired renal function given reported NSAID-induced renal failure in patients with decreased renal function.**

Pregnancy

It is not known what effects ixazomib has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner.

Nonsterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following:

- **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 from the time of signing of the informed consent form through 90 days after the last dose of study drug, or**
- **Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation 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:

- **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, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)**

6.1.5 Management of Clinical Events *(if applicable)*

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

Prophylaxis Against Risk of Reactivation of Herpes Infection

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

Nausea and/or Vomiting

Standard anti-emetics, including 5-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 deficit should be corrected before initiation of study drug and during treatment.

Diarrhea

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

Erythematous Rash With or Without Pruritus

As with bortezomib, rash with or without pruritus has been reported with ixazomib, primarily at the higher doses tested and when given with agents where rash is an overlapping toxicity. The rash may range from limited erythematous areas, macular and/or small papular bumps that may or may not be pruritic over a few areas of the body, to a more generalized eruption that is predominately on the trunk or extremities. Rash has been most commonly characterized as maculopapular or macular. To date, when it does occur, rash is most commonly reported within the first 3 cycles of therapy. The rash is often transient, self-limiting, and is typically Grade 1 to 2 in severity.

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

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

Thrombocytopenia

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

Neutropenia

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

Fluid Deficit

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

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

Hypotension

Symptomatic hypotension and orthostatic hypotension with or without syncope have been reported with ixazomib. Blood pressure should be closely monitored while the patient is on study treatment and fluid deficit should be corrected as needed, especially in the setting of concomitant symptoms such as nausea, vomiting, diarrhea, or anorexia. Patients taking medications and/or diuretics to manage their blood pressure (for either hypo- or hypertension)

should be managed according to standard clinical practice, including considerations for dose adjustments of their concomitant medications during the course of the trial. Fluid deficit should be corrected before initiation of study drug and as needed during treatment to avoid dehydration.

Posterior Reversible Encephalopathy Syndrome

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

Transverse Myelitis

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

6.1.6 Adverse Event List for Rituximab

Anticipated Drug Toxicities

The following safety data on rituximab related adverse events has been compiled from 315 patients who were treated in 5 single agent studies.

Infusion Related Events

Rituximab is associated with hypersensitivity reactions, which may respond to adjustments in the infusion rate. An infusion related symptom complex consisting of fever and chills/rigors occurred in the majority of patients during the first rituximab infusion. Other frequent infusion related symptoms include nausea, urticaria, fatigue, headache, pruritus, bronchospasm, dyspnea, sensation of tongue or throat swelling (angioedema), rhinitis, vomiting, hypotension, flushing, and pain at disease sites. These reactions have generally occurred within 30 minutes to 2 hours of beginning the first infusion, and resolved with slowing or interruption of the rituximab infusion and with supportive care (IV saline, diphenhydramine, famotidine or cimetidine, acetaminophen, glucocorticoids). The incidence of infusion related events decreased from 80% (7% Grade 3/4) during the first infusion to approximately 40% (5% to 10% Grade 3/4) with subsequent infusions. Mild to moderate hypotension requiring interruption of rituximab infusion with or without administration of IV saline occurred in 10% of patients. Isolated occurrences of severe reactions requiring epinephrine have been reported in patients receiving rituximab for other indications. Angioedema was reported in 13% of patients, and was serious in one patient. Bronchospasm occurred in 8% of patients; one quarter of these patients were treated with bronchodilators. A single report of bronchiolitis obliterans was noted.

Immunologic Events

Rituximab induced B-cell depletion in 70 to 80% of patients, and was associated with decreased serum immunoglobulins in a minority of patients. The incidence of infection does not appear to be increased. During the treatment period, 50 patients in the pivotal trial developed 68 infectious events; 6 (9%) were grade 3 in severity, and none were Grade 4 events. Of the 6 serious infectious events, none were associated with neutropenia. The serious bacterial events included sepsis due to Listeria (n=1), staphylococcal bacteremia (n=1), and polymicrobial sepsis (n=1). In the post-treatment period (30 days to 11 months following the last dose), bacterial infections included sepsis (n=1); significant viral infections included herpes simplex infections (n=2) and herpes zoster (n=3). The following immune serious adverse events have been reported to occur rarely (<0.1%) in patients following completion of rituximab infusions: arthritis, disorders of blood vessels (vasculitis, serum sickness and lupus-like syndrome), lung disorders including pleuritis and scarring of the lung (bronchiolitis obliterans), eye disorders (uveitis and optic neuritis), and severe bullous skin reactions (including toxic epidermal necrolysis and pemphigus) that may result in fatal outcomes. Patients may have these symptoms alone or in combination with rash and polyarthritis.

Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death has been reported in some patients with hematologic malignancies treated with rituximab. The majority of patients received rituximab in combination with chemotherapy. The median time to the diagnosis of hepatitis was approximately 4 months after the initiation of rituximab and approximately one month after the last dose.

Retreatment Events

Twenty-one patients have received more than one course of rituximab. The percentage of patients reporting any adverse event upon retreatment was similar to the percentage of patients reporting adverse events upon initial exposure. The following events were reported more frequently in retreated participants: asthenia, throat irritation, flushing, tachycardia, anorexia, leukopenia, thrombocytopenia, anemia, peripheral edema, dizziness, depression, respiratory symptoms, night sweats and pruritus.

Hematologic Events

In clinical trials, Grade 3 and 4 cytopenias were reported in 48% of patients treated with rituximab including: lymphopenia (40%), neutropenia (6%), leukopenia (4%), anemia (3%), and thrombocytopenia (2%). The median duration of lymphopenia was 14 days (range, 1 to 588 days) and of neutropenia was 13 days (range, 2 to 116 days). A single occurrence of transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following rituximab therapy were reported.

In addition, there have been a limited number of post marketing reports of prolonged pancytopenia, marrow hypoplasia, and late onset neutropenia (defined as occurring 40 days after the last dose of rituximab) in patients with hematologic malignancies. In reported cases of late

onset neutropenia (NCI-CTC Grade 3 and 4), the median duration of neutropenia was 10 days (range 3 to 148 days). Documented resolution of the neutropenia was described in approximately one-half of the reported cases; of those with documented recovery, approximately half received growth factor support. In the remaining cases, information on resolution was not provided. More than half of the reported cases of delayed onset neutropenia occurred in patients who had undergone prior autologous bone marrow transplantation. In an adequately designed, controlled, clinical trial, the reported incidence of NCI-CTC Grade 3 and 4 neutropenia was higher in patients receiving rituximab in combination with fludarabine as compared to those receiving fludarabine alone (76% [39/51] vs. 39% [21/53]).

Cardiopulmonary Events

Patients with pre-existing cardiac conditions, including arrhythmia and angina have had recurrences of these cardiac events during rituximab infusions. Four patients developed arrhythmias during rituximab infusion. One of the four patients discontinued treatment because of ventricular tachycardia and supraventricular tachycardias. The other three patients experienced trigeminy (1) and irregular pulse (2) and did not require discontinuation of therapy. Angina was reported during infusion and myocardial infarction occurred 4 days post-infusion in one participant with a history of myocardial infarction. In rare cases, severe and fatal cardiopulmonary events, including hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, and cardiogenic shock have occurred. Nearly all-fatal infusion-related events occurred in association with the first infusion.

Potential for fatal infusion reactions

In post marketing studies, rare events of tumor lysis syndrome have been reported in patients who had a high number of circulating malignant cells (>25,000/ul), with a rapid reduction in tumor volume, renal insufficiency, hyperkalemia, hypocalcemia, hyperuricemia, and hyperphosphatemia noted in these patients. For additional details, and updates see current rituximab package insert. In rare cases, severe and fatal cardiopulmonary events, including hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, and cardiogenic shock, have occurred. Nearly all-fatal infusion-related events occurred in association with the first infusion.

Prevention and management of abrupt increases in serum IgM and viscosity following Rituximab use in patients with Waldenström's macroglobulinemia

Abrupt and paradoxical increases in IgM levels have been reported with the use of rituximab in patients with Waldenström's macroglobulenemia, which may aggravate hyperviscosity and contribute to hyperviscosity related symptoms. Plasmapheresis is strongly encouraged for those patients at increased risk for hyperviscosity. Rituximab will be omitted for Cycles 1 and 2 in all patients.

6.1.7 Adverse Event List for Dexamethasone

Fluid and electrolyte disturbances: sodium retention; fluid retention; congestive heart failure in susceptible patients; potassium loss; hypokalemic alkalosis; hypertension; hypotension or shock-like reaction.

Musculoskeletal: muscle weakness; steroid myopathy; loss of muscle mass; osteoporosis; vertebral compression fractures; aseptic necrosis of femoral and humeral heads; pathologic fracture of long bones; tendon rupture.

Gastrointestinal: peptic ulcer with possible subsequent perforation and hemorrhage; perforation of the small and large bowel, particularly in patients with inflammatory bowel disease; pancreatitis; abdominal distention; ulcerative esophagitis.

Dermatologic: impaired wound healing; thin fragile skin; petechiae and ecchymoses; erythema; increased sweating; may suppress reactions to skin tests, burning or tingling, especially in the perineal area (after i.v. injection), other cutaneous reactions such as allergic dermatitis, urticaria, angioneurotic edema.

Neurological: convulsions; increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment; vertigo; headache; psychic disturbances.

Endocrine: menstrual irregularities; development of cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetes; hirsutism.

Ophthalmic: posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos; retinopathy of prematurity.

Cardiovascular: myocardial rupture following recent myocardial infarction; hypertrophic cardiomyopathy in low birth weight infants.

Metabolic: negative nitrogen balance due to protein catabolism.

Other: anaphylactoid or hypersensitivity reactions, thromboembolism, weight gain, increased appetite, nausea, malaise, hiccups.

The following additional adverse reactions are related to parenteral corticosteroid therapy: rare instances of blindness associated with intralesional therapy around the face and head; hyperpigmentation or hypopigmentation; subcutaneous and cutaneous atrophy; sterile abscess; post-injection flare (following intra-articular use); Charcot-like arthropathy.

6.2Toxicity Management and Dose Modifications/Delays

6.2.1 Ixazomib

Treatment with **ixazomib** will use a cycle length of 28 days during induction and 8 weeks during maintenance. For a new cycle of treatment to begin, the patient must meet the following criteria:

- ANC must be ≥ 1,000/mm3.
- Platelet count must be ≥ 75,000/mm3.
- All other non-hematologic toxicity (except for alopecia) must have resolved to ≤ Grade 1 or to the patient's baseline condition

Transfusion of blood products and G-CSF administration is not permissible on treatment days to meet the above requirements. If the patient fails to meet the above-cited criteria for initiation of the next cycle of treatment, dosing of ixazomib, rituximab, and dexamethasone should be delayed for 1 week. At the end of that time, the patient should be re-evaluated to determine whether the criteria have been met. If the patient continues to fail to meet the above-cited criteria, delay therapy and continue to re evaluate. The maximum delay before treatment should be discontinued will be 28 days or at the discretion of the Principal Investigator.

For dosing recommendations upon recovery, refer to Table 6-2 and Table 6-3.

Table 6-1 MLN908 Dose Adjustments

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

6.2.1.1 Dose Reductions for Hematologic Toxicities

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

Table 6-2 Ixazomib **Dose Adjustments for Hematologic Toxicities**

Ixazomib can be held for maximum of 28 days except at discretion of PI

Criteria	Action
Within-Cycle Dose Modifications If platelet count ≤ 30 × 109/L or ANC ≤ 0.50 × 109/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 (see Section 6.2.1) on at least 2 occasions. Upon recovery, ixazomib may be reinitiated with 1 dose level reduction.

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

Table 6-2 Ixazomib **Dose Adjustments for Hematologic Toxicities**
Ixazomib can be held for maximum of 28 days except at discretion of PI

Criteria	Action
Dose Modifications for Subsequent Treatment Cycles	
Delay of > 2 weeks in the start of a subsequent cycle due to lack of toxicity recovery as defined in Section 6.3.1.	Hold ixazomib until resolution as per criteria Section 6.2.
ANC < 1.0 × 109/L, platelet count < 75 × 109/L, or other nonhematologic toxicities > Grade 1 or not to the patient's baseline condition	Upon recovery, reduce ixazomib 1 dose level. The maximum delay before treatment should be discontinued will be 28 days 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,: If dose was reduced within the cycle, start the next cycle at that same dose. If due to toxicity timing, ie, after Day 15 dosing thus a dose reduction was not required at that point in the cycle, reduce ixazomib by 1 dose level at the start of that cycle. Do not reduce the dose both within a cycle and at the start of the cycle for the same most severe toxicity.

6.2.1.2 Dose Reductions for Non-Hematologic Toxicities

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

Ixazomib can be held for maximum of 28 days except at discretion of PI

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 6.6	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 6.6
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

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

Ixazomib can be held for maximum of 28 days except at discretion of PI

Adverse Event (Severity)	Action on Study Drug	Further Considerations
Grade 4 nonhematologic toxicities judged to be related to study drug	• Consider permanently discontinuing study drug	Exceptions are cases in which the investigator determines the patient is obtaining a clinical benefit

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

6.2.1.3 Missed Doses

Missed doses will not be replaced during a cycle. If a participant misses more than 2 doses of any cycle for reasons other than toxicity, the participant will be discontinued.

6.2.1.4 Changes in Body Surface Area (BSA)

Dose adjustments do not need to be made based on BSA changes.

6.2.1.5 Management of Adverse Events due to Rituximab

In the event that patients experience a fever spike (>101° F), rigors, mucosal congestion or edema, or a decline in blood pressure (>30 mm systolic drop) during infusion with rituximab, the infusion should be temporarily discontinued and the patient observed. When the patient has recovered, the infusion should be restarted at half the previous rate. Treatment of infusion-related symptoms with additional IV diphenhydramine, acetaminophen, IV corticosteroids, IV cimetidine or famotidine is recommended. Additional treatment with bronchodilators or IV saline may be indicated. Medications for treatment of hypersensitivity reactions, such as epinephrine, antihistamines, famotidine or cimetidine, and corticosteroids should be available for immediate use in the event of a reaction during administration. Infusions should be discontinued in the event of serious or life-threatening cardiac arrhythmias. Patients who develop clinically significant arrhythmias should undergo cardiac monitoring during and after subsequent infusions of rituximab. Patients with pre-existing cardiac conditions including arrhythmias and angina have had recurrences of these events during rituximab therapy and should be monitored throughout the infusion and immediate post-infusion period.

No dose reductions of rituximab will be permitted in this study. However, for patients who experience toxicities, delay in whole or in part for rituximab will be permitted. In the event a patient cannot receive their intended rituximab infusion due to an infusion related reaction or toxicity to rituximab, then their therapy may be delayed for up to 7 days. Patients who experience infusion related reactions and are unable to complete their rituximab therapy on the day they experience such a reaction, may be rescheduled to return to receive the balance of their therapy within 7 days. The timing for future rituximab infusions will remain on track should a patient experience delay in receiving therapy. Patients who experience an anaphylactic reaction

or are unable to tolerate rituximab will have their rituximab omitted, but continue receiving therapy otherwise as per protocol. Plasmapheresis is strongly encouraged for those patients at increased risk for hyperviscosity. Rituximab will be omitted for Cycles 1 and/or 2 in all patients.

CBC and differential will be obtained regularly as indicated in study calendar. Erythropoietin and transfusion support are permitted. Same day treatment with platelets is allowed as long as eligibility is met. Drug toxicities will be reported using common toxicity criteria.

Carriers of hepatitis B should be closely monitored for clinical and laboratory signs of active HBV infection and for signs of hepatitis throughout their study participation. Any participant who develops active HBV infection or hepatitis should not be treated with any further rituximab therapy.

6.2.1.6 Modification of Rate for Infusion of Rituximab

In the event that patients develop an infusion related or hypersensitivity reaction to rituximab then the rate of drug administration is altered as described above in "Management of Adverse Events due to rituximab". The total dose administered remains the same in such cases. In the event of serious or life threatening reactions, the infusion should be terminated and such adverse events reported**.** In the event of serious or life threatening events attributed to rituximab, patients may be removed from this study after consultation with the overall or institutional protocol chairperson.

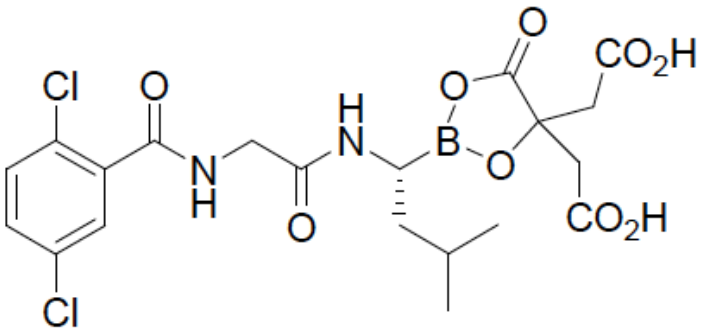
7.DRUG FORMULATION AND ADMINISTRATION

7.1Ixazomib

7.1.1 Description

Research Name	MLN9708
Chemical Name	2,2'-{2-[(1R)-1-({[(2,5-dichlorobenzoyl)amino]acetyl}amino)-3-methylbutyl]-5-oxo-1,3,2-dioxaborolane-4,4-diyl}diacetic acid
Common name	2,2'-{2-[(1R)-1-({[(2,5-dichlorobenzoyl)amino]acetyl}amino)-3-methylbutyl]-5-oxo-1,3,2-dioxaborolane-4,4-diyl}diacetic acid
Proprietary Name	Not available
USAN Name	Ixazomib citrate
CAS Registry Number	1239908-20-3
Classification	Proteasome inhibitor (as the boronic acid).
Molecular Formula	$C_{20}H_{23}BCl_2N_2O_9$
Molecular Weight	517.12

Figure 7-1 Structure of ixazomib



7.1.2 Form

All later phase studies are conducted with the Capsule formulation. The Ixazomib Capsule formulation consists of the Ixazomib drug substance and the inactive ingredients microcrystalline cellulose, talc, and magnesium stearate in a hard gelatin. Seven different capsule strengths have been developed: 0.2-, 0.5-, 2.0-, 2.3-, 3.0-, 4.0-, and 5.5 mg; each capsule strength has a unique color. Dosage strength is stated as the active boronic acid (MLN2238). Ixazomib Capsules are individually packaged in foil-foil blisters with a paper backing for child resistance. The study drug **ixazomib** capsules will be provided by Millennium. The study drug will be labeled and handled as open-label material, and packaging labels will fulfill all requirements specified by governing regulations.

7.1.3 Storage

Ixazomib capsules should be stored unopened at 2°C to 8°C (36°F-46°F). The capsules are individually packaged in cold form foil-foil blisters in a child-resistant package. The 2.3-, 3.0-, and 4.0 mg capsules are supplied as a 1 x 3 blister card in a child-resistant cardboard wallet. The permissible storage condition excursion range is 8°C to 40°C for a maximum period of 30 days; and from 0-50°C for up to 3 days.

7.1.4 Handling

Ixazomib drug product is a cytotoxic anticancer drug. As with other potentially toxic compounds, caution should be exercised when handling Ixazomib. Please refer to published guidelines regarding the proper handling and disposal of cytotoxic agents. Ixazomib Capsules must be administered as intact capsules and are not intended to be opened or manipulated in any way.

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

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

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

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.

7.1.5 Availability

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

Ixazomib capsules should be stored unopened at 2°C to 8°C (36°F-46°F). The capsules are individually packaged in cold form foil-foil blisters in a child-resistant package. 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.

7.1.6 Ordering

Ixazomib will be ordered directly from Millennium Pharmaceuticals via a drug order form that is faxed from the pharmacist.

7.1.7 Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using the NCI Drug Accountability Record or another comparable drug accountability form. (See the CTEP website at http://ctep.cancer.gov/protocolDevelopment for the "Policy and Guidelines for Accountability and Storage of Investigational Agents" or to obtain a copy of the drug accountability form.)

Millennium Pharmaceuticals and the Pharmacy will maintain records of each shipment of investigational product. The records will document shipment dates, batch numbers, and quantity of vials contained in the shipment. Upon receipt of the investigational product, the designated recipient at the study site will inspect the shipment, verify the number and condition of the vials, and prepare an inventory or drug accountability record.

Drug accountability records must be readily available for inspection by representatives of Millennium Pharmaceuticals and by regulatory authorities.

7.1.8 Destruction and Return

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

7.2Rituximab

7.2.1 Description

Rituximab is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 cell surface antigen. The antibody is an IgG kappa immunoglobulin containing murine light- and heavy-chain variable region sequences and human constant region sequences. Rituximab is a composed of two heavy chains of 451 amino acids and two light chains of 213 amino acids (based on cDNA analysis) and has an approximate molecular weight of 145 kD. Rituximab has a binding affinity for the CD20 antigen of approximately 8 nM. The chimeric anti-CD20 antibody is produced by mammalian cell (Chinese Hamster ovary) suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product. Rituximab is purified by affinity and ion exchange chromatography. The purification process includes specific viral inactivation and removal procedures.

Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death has been reported in some patients with hematologic malignancies treated with rituximab. The majority of patients received rituximab in combination with chemotherapy. The median time to the diagnosis of hepatitis was approximately 4 months after the initiation of rituximab and approximately one month after the last dose.

7.2.2 Form

Rituximab is supplied as a sterile, colorless, preservative free liquid concentrate for intravenous (IV) administration. Rituximab is supplied at a concentration of 10 mg/ml in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials. The product is formulated for IV administration in 9mg/ml sodium chloride, 7.35-mg/mL sodium citrate dehydrate, 0.7 mg/mL polysorbate 80, and sterile water for injection. The pH is adjusted to 6.5.

7.2.3 Storage and Stability

Rituximab vials are stable at 2°-8° C. Vials of rituximab beyond expiration date on the carton should not be used. Rituximab vials should be protected from direct sunlight.

7.2.4 Handling

Rituximab is diluted to a final concentration of 1 to 4 mg/ml into an infusion bag containing either 0.9% sodium chloride USP or 5% dextrose in water USP. Rituximab solutions for infusion are stable at 2° to 8° C for 24 hours and at room temperature for an additional 12 hours. No incompatibilities between rituximab and polyvinylchloride or polyethylene bags have been reported.

7.2.5 Availability

Rituximab is commercially available.

7.2.6 Administration

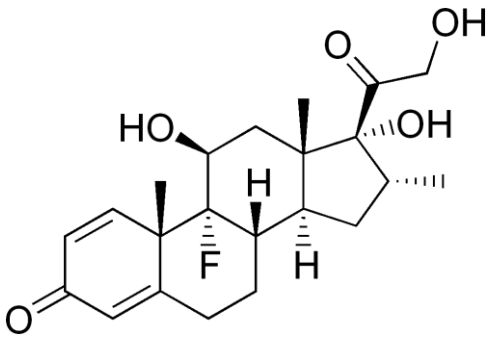
Rituximab is administered intravenously. To prevent infusion related or hypersensitivity events, rituximab is not to be administered as an intravenous push or bolus. See section 5.2.2.6 for details on administration of rituximab.

7.3Dexamethasone

7.3.1 Description

Dexamethasone is a potent synthetic member of the glucocorticoid class of steroid hormones. It acts as an anti-inflammatory and immunosuppressant. Its potency is about 20-30 times that of hydrocortisone and 4-5 times of prednisone.

Figure 7-2 Structure of dexamethasone



7.3.2 Form

Each mL of clear, colorless sterile solution contains: dexamethasone sodium phosphate equivalent to dexamethasone phosphate 4 mg (equal to 3.33 mg of dexamethasone or roughly about 100 mg of hydrocortisone). Non-medicinal ingredients: creatinine, sodium citrate, sodium hydroxide (to adjust pH) and water for injection with sodium bisulfite, methylparaben, and propylparaben are added as preservatives.

7.3.3 Storage and Stability

Store below 25°C. Do not freeze. Protect from light.

7.3.4 Availability

Dexamethasone is a commercially available agent.

7.3.5 Administration

Patients will receive dexamethasone 20 mg IV, with each infusion of ixazomib and rituximab. Dexamethasone should be given prior to ixazomib and rituximab. The administration of IV Dexamethasone will suffice for steroid for premedication for rituximab. 20 mg oral dexamethasone may be substituted in the event of a drug supply shortage of IV dexamethasone and on days 8 and 15 of induction and maintenance for dosing outside of clinic. Administration method will be documented.

7.3.6 Contraindications for Dexamethasone therapy

Dexamethasone will be omitted from therapy in the following circumstances:

- History of tuberculosis or other granulomatous disease
- Systemic fungal infection
- History of or development of uncontrollable steroid related glucose intolerance
- History of or development of steroid related hypersensitivity
- Intolerance due to gastric and duodenal ulcers despite adequate upper gastrointestinal prophylactic therapy
- Recipient of a live virus vaccine within 30 days

- Pregnancy and lactation
- Development of moderate to severe acute infections

In the event dexamethasone is omitted, patients will not be removed from study treatment and will continue to receive all other intended therapy on study.

7.4Study 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.

7.5Termination 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
- Other

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

8.CORRELATIVE/SPECIAL STUDIES

8.1Determination of MYD88 and CXCR4 mutational status

The MYD88 L265P mutational analysis will be assessed by allele-specific PCR and CXCR4 mutational analysis by Sanger sequencing. The Brigham & Women's Hospital Advanced Molecular Laboratory will perform the MYD88 mutational analysis. The CXCR4 mutational analysis and FcγRIIIA-158 polymorphisms analysis will be performed by the Bing Center for Waldenström's Macroglobulinemia Research Laboratory.

9.STUDY CALENDAR

	Screening ≤30 days from study entry	Induction Phase q28 days +/- 3 Days*,**						Inter-phase Visit Within 4 weeks +/- 2 weeks of completion of Cycle 6 of induction	Maintenance Phase (Beginning 8 weeks +/- 2 weeks after Induction C6D1) q 8 weeks +/- 2 weeks			Off Treatment Visit within 4 weeks +/- 2 weeks of completion of all treatment or removal from trial	Follow-up Q6 months +/- 2 weeks for 2 years[6]
		Cycles 1 and 2			Cycles 3-6				Cycles 1-6				
		D1	D8	D15	D1	D8[8]	D15[8]		D1**	D8	D15		
Dexamethasone		X	X	X	X	X	X		X	X	X		
Ixazomib		X	X	X	X	X	X		X	X	X		
Rituximab					X				X				
Informed consent	X												
Physical exam (Ht, Wt, BSA, VS)	X	X			X			X	X			X	X
History	X	X						X	X			X	X
Concurrent meds	X	X			X			X	X			X	X
ECOG Performance Status	X	X			X			X	X			X	X
CBC w/diff, platelets	X	X	X	X	X	X	X	X	X			X	X
Serum chemistry[1,]	X	X	X	X	X	X	X	X	X[1]			X	X
Coagulation Profile (PT, PTT, INR)	X												
Quantitative IgM, IgA, IgG	X	X			X			X	X			X	X
SPEP and immunofixation[2]	X	X			X			X	X			X	X
Beta-2-Microglobulin	X												
B-HCG[3]	X												
Hepatitis B and C Screening	X												
MYD88 L265P status bone marrow (PCR)	X							X				X	
MYD88 L265P status peripheral blood (qPCR)	X[7]												
CXCR4 mutational status (Sanger)	X												
Adverse event evaluation	X	X			X			X	X			X	
Neuropathy Assessment	X	X			X			X	X			X	
CT scan w/ contrast Chest/Abdomen/Pelvis[5]	X[4]							X[5]				X[5]	
Bone Marrow Biopsy and Aspiration[2]	X[4]							X				X	

*: Peripheral Neuropathy questionnaire and labs do not need to be repeated if Day 1 of induction treatment within 10 days of screening. If labs are repeated on C1D1 they must be reviewed prior to study drug administration and meet eligibility.

**: For criteria for administration of treatment see Section 6.2

1: Comprehensive chemistry panel: Albumin, total bilirubin, BUN, creatinine, calcium, chloride, glucose, potassium, total protein, sodium, SGOT, SGPT, alkaline phosphatase, magnesium

2: Bone Marrow Biopsy and Aspiration will be required at Screening, Interphase visit, and Off-Treatment Visit. May be Repeated at other time points to confirm a suspected complete remission and at the Principal Investigator's discretion

3: Serum pregnancy test for women of childbearing potential

4: If done within 90 days of screening, this will not be required at the screening visit

5: Repeat to assess disease response or confirm a suspected complete remission if participant had lymphadenopathy, hepatosplenomegaly, or an extramedullary mass at baseline defined as adenopathy >1.5 cm in any axis, and splenomegaly >15 cm in the craniocaudal axis.

6. Follow-up visits will be required every 6 months +/- 2 weeks after EOT visit. 3 month follow-up visits are recommended.

7. MYD88 L265P mutational status by qPCR at screening and, if mutant, subsequently every 3 months while on therap.

8. Safety Laboratories do not need to be performed on Day 8 and 15 of Induction Cycles 4-6, or any Maintenance cycles.

10.MEASUREMENT OF EFFECT

10.1Response Criteria

Response criteria are based on modified response criteria updated at the Third International Workshop on Waldenstrom's macroglobulinemia (Kimby 2006; Treon 2011).

For participants who undergo TPE (total plasmapheresis), IgM will be considered unevaluable for 4-6 weeks following the last TPE treatment. For response assessment, post-pheresis IgM values will not be considered as nadir values.

When rituximab induced IgM flare is suspected, serum IgM response will be determined to be unevaluable by the investigator and not considered to be progressive disease.

Complete Response (CR): A complete response (CR) is defined as having resolution of all symptoms, normalization of serum IgM levels with complete disappearance of IgM paraprotein by immunofixation, and resolution of any adenopathy or splenomegaly. A near CR (nCR) is defined as fulfilling all CR criteria in the presence of positive immunofixation test for an IgM paraprotein.

Very Good Partial Response (VGPR): is defined as >90% reduction in serum IgM levels.

Partial Response (PR): Partial response (PR) is defined as achieving a $\geq$50% reduction in serum IgM levels.

Minor Response (MR): A minor response (MR) is defined 25-49% reduction in serum IgM levels.

Progressive Disease (PD): Progressive disease (PD) is defined as occurring when a greater than 25% increase in serum IgM and an absolute 500mg/dL increase in IgM level occurs from the lowest attained response value(except as specfied above) or progression of clinically significant disease related symptom(s). When PD is suspected on the basis of increasing serum IgM, repeat of these studies within 2 $\pm$ 1 week(s) will be required to confirm PD.

Stable Disease (SD): Stable disease is defined as having < 25% change in serum IgM levels, in the absence of new or increasing adenopathy or splenomegaly and/or other progressive signs or symptoms of WM.

10.2Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started, except in cases of TPE, specified in section 10.1). The participant's best response assignment will depend on the achievement of both measurement and confirmation criteria.

10.3Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for an objective response i.e. CR, PR or MR (whichever is first recorded) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started (except in cases of TPE, specified in section 10.1).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the protocol treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started (except in cases of TPE, specified in section 10.1).

10.4Time to Progression

Time to Progression (TTP) is defined as the duration of time from start of treatment to time of disease progression as defined in section 10.1. Death from any cause or initiation of a new anti-neoplastic therapy will also be considered a progression event.

10.5 Time to Next Therapy

Time to Next Therapy (TNT) is defined as the duration from start of protocol treatment to time of initiation of any new anti-neoplastic therapy, including radiation or intrathecal therapy.

11.ADVERSE EVENT REPORTING REQUIREMENTS

11.1Definitions

11.1.1Adverse Event (AE) 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.
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.

11.1.2 Serious adverse event (SAE) 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** (see clarification in the paragraph below on planned hospitalizations).
- 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/mm3 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.

11.1.3 Expectedness

Adverse events can be "Expected" or "Unexpected."

11.1.3.1 Expected adverse event

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered

expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

Refer to Section 6.1 for a listing of expected adverse events associated with the study agent(s).

11.1.3.2 Unexpected adverse event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

11.1.4 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment.

11.2Procedures for AE and SAE Recording and Reporting

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

AEs which are serious must be reported to Millennium Pharmacovigilance (or designee) from the first dose of study drug through 30 days after administration of the last dost of ixazomib. Any SAE that occurs at any time after completion of **ixazomib** treatment or after the designated follow-up period that the sponsor-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).

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

Since this is an investigator-initiated study, the principal investigator Jorge J. Castillo, MD, also referred to as the sponsor-investigator, is responsible for reporting serious adverse events (SAEs) to any regulatory agency and to the sponsor- investigator's EC or IRB.

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 of the sponsor-investigator's observation or awareness of the event

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

See below for contact information for the reporting of SAEs to Millennium Pharmacovigilance. The sponsor-investigator must fax or email the SAE Form per the timelines above. A sample of an SAE Form will be provided. The SAE report must include at minimum:

- Event term(s)
- Serious criteria
- Intensity of the event(s): **Sponsor-investigator's 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): **Sponsor-investigator's or sub-investigator's determination of the relationship of the event(s) to study drug administration.**

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

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

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

Relationship to all study drugs for each SAE will be determined by the investigator or sub-

investigator by responding yes or no to the question: Is there a reasonable possibility that the AE is associated with the study drug(s)?

Sponsor-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

Fax Number: 1-800-963-6290
Email: TakedaOncoCases@cognizant.com

Suggested Reporting Form:

- SAE Report Form (provided by Millennium)
- US FDA MedWatch 3500A: http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm

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 after the last dose**, she must inform the investigator immediately and permanently discontinue study drug. The sponsor-investigator must immediately fax a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 8.2). 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 sponsor-investigator must also immediately fax a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 8.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

11.3Reporting to the Institutional Review Board (IRB)

Investigative sites within DF/HCC will report all serious adverse events directly to the DFCI Office for Human Research Studies (OHRS).

11.4Reporting to the Food and Drug Administration (FDA)

The DF/HCC Overall Principal Investigator, as holder of the IND, will be responsible for all communication with the FDA. The DF/HCC Overall Principal Investigator will report to the FDA, regardless of the site of occurrence, any adverse event that is serious, unexpected and reasonably related (i.e., possible, probable, definite) to the study treatment.

Unexpected fatal or life-threatening experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 7 calendar days after initial receipt of the information.

All other serious unexpected experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 15 calendar days after initial receipt of the information.

Events will be reported to the FDA by telephone (1-800-FDA-1088) or by fax (1-800-FDA-0178) using Form FDA 3500A (Mandatory Reporting Form for investigational agents) or FDA Form 3500 (Voluntary Reporting Form for commercial agents). Forms are available at http://www.fda.gov/medwatch/getforms.htm.

11.5Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

11.6Pregnancy Reporting

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor-investigator must immediately fax a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 11.2). 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 sponsor-investigator must also immediately fax a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 11.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

11.7Monitoring of Adverse Events and Period of Observation

All adverse events, both serious and non-serious, and deaths that are encountered from initiation of study intervention, throughout the study, and within 30 days of the last study intervention should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up. The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification.

For some SAEs, the study sponsor (Dr. Jorge J. Castillo) or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study.

11.8 Product Complaints

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

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

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to Millennium Pharmacovigilance (refer to Section 8.2).

12.DATA AND SAFETY MONITORING

12.1Data Reporting

12.1.1 Method

The QACT will collect, manage, and monitor data for this study.

12.1.2 Data Submission

The schedule for completion and submission of case report forms (paper or electronic) to the QACT is as follows:

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration with QACT
On Study Form	Within 14 days of registration
Baseline Assessment Form	Within 14 days of registration
Treatment Form	Within 10 days of the last day of the cycle
Adverse Event Report Form	Within 10 days of the last day of the cycle
Response Assessment Form	Within 10 days of the completion of the cycle required for response evaluation
Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason

Follow up/Survival Form	Within 14 days of the protocol defined follow up visit date or call

12.2Safety Meetings

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator and study team.

The DSMC will meet quarterly and/or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days for Phase I or II protocols; for gene transfer protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the DF/HCC Overall Principal Investigator (or Protocol Chair) or DF/HCC. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, Good Clinical Practice (GCP), and any applicable regulatory requirements.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

13.REGULATORY CONSIDERATIONS

13.1Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the

IRB. The DF/HCC Overall Principal Investigator (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

13.2Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

13.3Ethics and Good Clinical Practice (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
    - Title 21 Part 50 – Protection of Human Subjects www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
    - Title 21 Part 54 – Financial Disclosure by Clinical Investigators www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
    - Title 21 Part 56 – Institutional Review Boards www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html
    - Title 21 Part 312 – Investigational New Drug Application www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html
- State laws
- DF/HCC research policies and procedures: http://www.dfhcc.harvard.edu/clinical-research-support/clinical-research-unit-cru/policies-and-procedures/

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

13.4Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

13.5Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

13.6IND Annual Reports

The sponsor investigator or his designee will submit the annual report for this PI-initiated trial within 60 days of the IND anniversary date in accordance with 21 CFR 312.33. The data elements that are to be submitted in the report are provided in 21 CFR 312.33. The Annual Report should be filed in the study's Regulatory Binder.

14.STATISTICAL CONSIDERATIONS

14.1Study Design/Endpoints

Following Fleming's single phase approach and with a one-sided alpha set at 0.05 and beta at 0.20 (80% power) assuming a null VGPR or better of 18% and a successful VGPR or better of 40%, we will need to accrue 23 participants. In a previous study, the combination of bortezomib, rituximab and dexamethasone induced VGPR or better of 35% [22]. If at least 9 participants are found to have a response of VGPR or better, the trial will be deemed a success and IDR will warrant further testing in patients with WM. Accounting for 10% of non-evaluable patients, the total sample size will be 26 patients. In addition, with a sample size of 26 participants, the probability of observing at least one adverse event will be 93% when the actual probability of this event is 10%. Counting 1 patient who was registered but never started, 27 patients were accrued to this study.

14.2Populations for analysis

The population for all safety analyses is the Safety Analysis Set (SAS). All participants who receive at least one dose of any test material during the study will be included in the SAS population and included in the safety analysis.

Participants will be included in the Full Analysis Set (FAS) for the primary assessment of efficacy. The FAS will include those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated.

The Per-Protocol Analysis Set (PPS) is defined as all participants from the FAS set who complete the study and are deemed to be protocol-compliant. To be protocol-compliant, a participant must not have any major protocol deviations during the study period. Protocol deviations will be identified prior to database lock and will be listed in the clinical study report. The PPS will be used for a secondary assessment of efficacy endpoints.

14.3Participant Disposition

The total number of participants screened, completed, and prematurely discontinued from the study will be summarized. The reason for termination for all participants who discontinued will also be presented. A listing of participants with major protocol deviations will also be presented.

14.4Participants Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented for all participants.

14.5Exposure to Investigational Material

Exposure to all test material will be tabulated by presenting number of days on study, defined as number of days from day of first dose to day of last infusion. Total amount of investigational material taken will also be presented.

14.6Safety Analysis

Safety evaluations will be presented by escalating dose and based on the incidence, intensity and type of adverse events (AEs).

All AEs occurring on study will be listed in by-participant data listings. A by-dose tabulation will be provided that enumerates AEs by maximum severity. Deaths, SAEs and events resulting in study discontinuation will be tabulated.

14.7Efficacy Analyses

Primary and secondary analyses will be performed in both the FAS and PPS populations and will include calculating the proportion of patients having an overall response (MR or better) and major response (CR or VG). Confidence intervals (95%) about these point estimates will be presented. Time to progression (TTP) and time to next therapy (TNT) as defined in sections 10.4, and 10.5, respectively will be estimated using Kaplan and Meier methodology with median time plus 25^{th} and 75^{th} percentile time to progression free survival along with 95% confidence intervals being provided, as appropriate. In addition, landmark analysis for 2 and 4 year progression free survival will be performed.

14.8Sample Size/Accrual Rate

Following Fleming's single phase approach and with a one-sided alpha set at 0.05 and beta at 0.20 (80% power) assuming a null VGPR or better of 18% and a successful VGPR or better of 40%, we will need to accrue 30 participants. In a previous study, the combination of bortezomib, rituximab and dexamethasone induced VGPR or better of 35% [22]. If at least 10 participants are found to have a response of VGPR or better, the trial will be deemed a success and IDR will warrant further testing in patients with WM. Accounting for 10% of non-evaluable patients, the total sample size will be 33 patients. In addition, with a sample size of 33 participants, the probability of observing at least one adverse event will be 97% when the actual probability of this event is 10%.

The accrual expectation is 2-3 patients per month with a total accrual time of 12-15 months.

14.9Stratification Factors

There will be no stratification employed in the current study.

14.10Analysis of Secondary Endpoints

The secondary objectives of determining the impact of MYD88 and CXCR4 gene mutations, and FcγRIIIA-158 polymorphisms in predicting overall and categorical response to treatment, as well as progression-free survival, will be assessed by presenting these outcomes by mutation/polymorphism type. If there are sufficient numbers in each category, appropriate inferential statistics may be performed. These analyses would be considered exploratory in nature.

14.11Evaluation of toxicity

All participants will be evaluable for toxicity from the time of their first treatment.

14.12Evaluation of response

All participants included in the study will be assessed for response to treatment according to criteria set forth in section 10.1.

15.PUBLICATION PLAN

Any formal presentation or publication of data from this trial may be published after review and comment by Millennium Pharmaceuticals and prior to any outside submission. Millennium Pharmaceuticals must receive copies of any intended communication in advance of publication (at least fifteen working days for presentational materials and abstracts and thirty working days for manuscripts). These requirements acknowledge Millennium Pharmaceuticals' responsibility to provide peer input regarding the scientific content and conclusions of such publications or presentations. Principal Investigator/Institution shall have the final authority to determine the scope and content of its publications, provided such authority shall be exercised with reasonable regard for the interests of Millennium Pharmaceuticals and, in accord with the trial contract and

shall not permit disclosure of Millennium Pharmaceuticals' confidential or proprietary information.

16.REFERENCES

1. Owen RG, Treon SP, Al-Katib A, et al. Clinicopathological definition of Waldenström's Macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenström's Macroglobulinemia. Semin Oncol 2003; 30: 110-115.
2. Waldenström J. Incipient myelomatosis or "essential" hyperglobulinemia with fibrinogenopenia - A new syndrome? Acta Med Scand 1944; 117: 216-47.
3. Treon SP, Gertz MA, Dimopoulos M, et al. Update on treatment recommendations from the Third International Workshop on Waldenstrom's Macroglobulinemia. Blood 2006; 107:3442-6.
4. Dimopoulos MA, Gertz MA, Kastritis E, et al. Update on treatment recommendations from the fourth international workshop on Waldenstrom's macroglobulinemia. J Clin Oncol 2008; 27:120-6
5. Treon SP. How I Treat Waldenstrom's Macroglobulinemia. Blood 2009a; 114(12) :2375-85.
6. Leleu X, Tamburini J, Roccaro A, et al. Balancing risk versus benefit in the treatment of Waldenström's Macroglobulinemia patients with nucleoside analogue-based therapy. Clin Lymphoma Myeloma 2009 Mar;9(1):71-3.
7. Treon SP, Emmanouilides C, Kimby E, et al. Extended rituximab therapy in Waldenström's Macroglobulinemia. Ann Oncol 2005a; 16:132-8.
8. Dimopoulos MA, Anagnostopoulos A, Zervas C, et al. Predictive factors for response to rituximab in Waldenstrom's macroglobulinemia. Clin Lymphoma 2005; 5:270-2.
9. Treon SP, Hansen M, Branagan AR, et al. Polymorphisms in FcγRIIIA (CD16) receptor expression are associated with clinical responses to Rituximab in Waldenstrom's Macroglobulinemia. J Clin Oncol 2005b; 23: 474-81.
10. Treon SP, Ioakimidis L, Soumerai JD, et al. Primary therapy of Waldenstrom's Macroglobulinemia with Bortezomib, Dexamethasone and Rituximab: Results of WMCTG Clinical Trial 05-180. J Clin Oncol 2009b; 27(23):3830-5.
11. Ghobrial IM, Xie W, Padmanabhan S, et al. Phase II trial of weekly bortezomib in combination with rituximab in untreated patients with Waldenström Macroglobulinemia. Am J Hematol. 2010;85(9):670-4.
12. Treon SP, et al. Prospective phase II clinical trial of carfilzomib, rituximab and dexamethasone (CARD) in Waldenström's Macroglobulinemia (WM). ASH Annual Meeting abstract, 2013.
13. Treon SP, Xu L, Yang G, et al. MYD88 L265P somatic mutation in Waldenström's macroglobulinemia. N Engl J Med 2012; 367(9): 826-33.
14. Ondrejka SL, Lin JJ, Warden DW, et al. MYD88 L265P Somatic Mutation: Its Usefulness in the Differential Diagnosis of Bone Marrow Involvement by B-Cell Lymphoproliferative Disorders. Am J Clin Pathol. 2013 Sep;140(3):387-94.
15. Cartron G, Dacheux L, Salles G, Solal-Celigny P, Bardos P, Colombat P, Watier H. Therapeutic activity of humanized anti-CD20 monoclonal antibody and polymorphism in IgG Fc receptor Fcgamma RIIIA gene. Blood. 2002; 99:754-8.
16. Poulain S, Roumier C, Decambron A, et al. MYD88 L265P mutation in Waldenstrom

macroglobulinemia. Blood. 2013 May 30;121(22):4504-11.
17. Varettoni M, Arcaini L, Zibellini S, et al. Prevalence and clinical significance of the MYD88 (L265P) somatic mutation in Waldenstrom's macroglobulinemia and related lymphoid neoplasms. Blood. 2013 Mar 28;121(13):2522-8.
18. Xu L, Hunter ZR, Yang G, et al. MYD88 L265P in Waldenström macroglobulinemia, immunoglobulin M monoclonal gammopathy, and other B-cell lymphoproliferative disorders using conventional and quantitative allele-specific polymerase chain reaction. Blood. 2013 Mar 14;121(11):2051-8.
19. Cao Y, Xu L, Liu X, et al. Whole Genome Sequencing Identifies Recurring Somatic Mutations in the C-Terminal Domain of CXCR4, Including a Gain of Function Mutation in Waldenstrom's Macroglobinemia. *Blood* (ASH Annual Meeting Abstracts) 2012. 120: abstract 2715.
20. Hunter Z, Xu L, Yang G, et al. Recurring activation mutations and somatic deletions revealed through whole genome sequencing in Waldenstrom's Macroglobulinemia. Hematological Oncol. 2013 June; 31(1S): abstract 093.
21. Weng WK, Levy R. Two Immunoglobulin G Fc receptor polymorphisms independently predict response to rituximab in patients with follicular lymphoma. J Clin Oncol 2003; 21:3940-3947.
22. Treon et al. The attainment of CR/VGPR is associated with significantly longer progression free survival in rituximab naïve WM patients undergoing rituximab based therapy, and is predicted by polymorphisms in FcγRIIIA-158. Br J Haematol, 2011.
23. Kyle R, Treon SP, Alexanian R, et al. Prognostic markers and criteria to initiate therapy in Waldenström's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenström's Macroglobulinemia. Semin Oncol. 2003; 30: 116-20.
24. Kimby E, Treon SP, Anagnostopoulos A. Dimopoulos M, Garcia-Sanz R et al. Update on recommendations for assessing response from the Third International Workshop onWaldenstrom's Macroglobulinemia. Clin Lymphoma Myeloma. 2006; 6(5): 380-3.

17.APPENDICES

Appendix A: Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Description	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active 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.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	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.

Screening/Off Study Induction/Maintenance Cycle_____ Day____

Appendix B: IDR Neuropathy Assessment Questionnaire

Patient Name:_____ MRN_____

Patient Signature:_____ Date_____

Please circle one (1) number to indicate how true each of the following statements has been for you in the past 7 days.

	None	A little bit	Somewhat	Quite a bit	Very much
I have numbness or tingling in my hands	0	1	2	3	4
I have numbness or tingling in my feet	0	1	2	3	4
I feel discomfort in my hands	0	1	2	3	4
I feel discomfort in my feet	0	1	2	3	4
I have joint pain or muscle cramps	0	1	2	3	4
I feel weak all over	0	1	2	3	4
I have trouble hearing	0	1	2	3	4
I get ringing or buzzing in my ears	0	1	2	3	4
I have trouble with buttons	0	1	2	3	4
I have trouble feeling the shape of small objects	0	1	2	3	4
I have trouble walking	0	1	2	3	4

Adapted from "Neurotoxicity Assessment Tool" Millennium. Cella DF, Tulsky DS, Gary G et al. The functional assessment of cancer therapy (FACT) scale: development and validation of the general measure. J Clin Oncol 1993:11(3):570-79. Calhoun EA, Fishman A, Roland PY et al. Validity and selective sensitivity of the FACT/GOG-Ntx. Abstract 1751. 36th Annual Meeting of the American Society of Clinical Oncology, May 2000, New Orleans, LA.