CLINICAL STUDY PROTOCOL

2018-1090

A Phase 2 Study of Ixazomib and Rituximab in Bruton's Tyrosine Kinase Inhibitor Resistant Mantle Cell Lymphoma

Indication:	Bruton's Tyrosine Kinase Inhibitor Resistant Mantle Cell Lymphoma
Phase:	Phase II

Protocol History

Original	21 February 2019
Revision 1	22 April 2019
Revision 2	13 May 2019
Revision 3	30 May 2019
Revision 4	29 July 2019

Investigator and Study Center:
Hun Ju Lee
M.D. Anderson Cancer Center
Department of Lymphoma & Myeloma
1515 Holcombe Blvd., Houston, TX 77030
713-794-1829

The principal investigator Hun Ju Lee 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.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

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

Abbreviation	Term
$5\text{-}HT_3$	5-hydroxytryptamine 3 serotonin receptor
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
API	active pharmaceutical ingredient
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
BTK	Bruton's tyrosine kinase
BUN	blood urea nitrogen
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 remission
CRM	continual reassessment method
CRP	C-reactive protein
CSF-1R	colony-stimulating factor 1 receptor

Abbreviation	Term
CT	computed tomography
C_{trough}	single-dose end of dosing interval (trough) concentration
CV	cardiovascular
CYP	cytochrome P_{450}
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

Abbreviation	Term
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
MRP2	Multidrug resistance-associated protein 2
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
OATP	organic-anion-transporting polypeptide
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
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

Abbreviation	Term
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
TLS	Tumor lysis syndrome
T_{max}	single-dose time to reach maximum (peak) concentration
UK	United Kingdom
ULN	upper limit of the normal range
US	United States
V_z	volume of distribution in the terminal phase
WBC	white blood cell
WHO	World Health Organization

1. BACKGROUND AND STUDY RATIONALE

1.1 Scientific Background

1.1.1 Disease Under Treatment

Mantle Cell Lymphoma

1.1.2 Ixazomib (MLN9708)

1.2 Preclinical Experience

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

1.3 Clinical Experience

Our group published the bortezomib in combination with rituximab and cyclophosphamide in heavily pretreated high risk MCL patient population. We had ORR of 74% with CR rates of 42%, we showed that no grade 3-4 neuropathy was noted in this population showing that proteasome inhibition plus anti CD20 antibody represents a reasonable regimen for MCL failing frontline therapy.[18] In another similar phase II study of rituximab, cyclophosphamide, bortezomib and dexamethasone in relapsed refractory MCL patients, Sonbol and colleagues at Mayo Clinic demonstrated robust overall response rate of 62% and complete remission rate of 19%, with acceptable safety profile.[19]

1.4 Pharmacokinetics and Drug Metabolism

After oral dosing, absorption of ixazomib is rapid with a median first time to maximum observed plasma concentration (T_{max}) of approximately 1 hour post dose. The plasma exposure (AUC) of ixazomib increases in a dose-proportional manner over a dose range of 0.2 to 10.6 mg based on population PK analysis. The absolute oral bioavailability (F) of ixazomib is estimated to be 58% based on population PK analysis. A high-fat meal reduced ixazomib C_{max} by 69% and AUC_{0-216} by 28%. This indicates that a high-fat meal decreases both the rate and extent of absorption of ixazomib. Therefore, ixazomib should be dosed at least 2 hours after food or 1 hour before food.

The steady-state volume of distribution of ixazomib is large and is estimated to be 543 L based on a population PK model. Based on in vitro plasma protein binding measurements on samples from clinical studies (Studies C16015 and C16018), ixazomib is highly bound to plasma proteins (99%). Ixazomib concentrations are higher in whole blood than in plasma, indicating

extensive partitioning of ixazomib into red blood cells, which are known to contain high concentrations of the 20S proteasome.

Metabolism appears to be the major route of elimination for ixazomib. In vitro studies indicate that ixazomib is metabolized by multiple cytochrome P450 (CYP) and non-CYP proteins. At concentrations exceeding those observed clinically (10 μM), ixazomib was metabolized by multiple CYP isoforms with estimated relative contributions of 3A4 (42.3%), 1A2 (26.1%), 2B6 (16.0%), 2C8 (6.0%), 2D6 (4.8%), 2C19 (4.8%), and 2C9 (<1%). At 0.1 and 0.5 μM substrate concentrations, which are closer to clinical concentrations of ixazomib following oral administration of 4 mg ixazomib, non-CYP mediated clearance was observed and seemed to play a major role in ixazomib clearance in vitro. These data indicate that at clinically relevant concentrations of ixazomib, non-CYP proteins contribute to the clearance of ixazomib and no specific CYP isozyme predominantly contributes to the clearance of ixazomib. Therefore, at clinically relevant concentrations of ixazomib, minimal CYP-mediated DDIs with a selective CYP inhibitor would be expected.

Ixazomib is neither a time-dependent inhibitor nor a reversible inhibitor of CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5. Ixazomib did not induce CYPs 1A2, 2B6, and 3A4/5 activity or corresponding immunoreactive protein levels. Thus, the potential for ixazomib to produce DDIs via CYP isozyme induction or inhibition is low.

Ixazomib is not a substrate of BCRP, MRP2 and OATPs. Ixazomib is not an inhibitor of P-gp, BCRP, MRP2, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1 and MATE2-K. Ixazomib is unlikely to cause or be susceptible to clinical DDIs with substrates or inhibitors of clinically relevant drug transporters.

The geometric mean terminal half-life ($t_{1/2}$) of ixazomib is 9.5 days based on population PK analysis. For both IV and oral dosing, there is an approximately average 3-fold accumulation (based on AUC) following the Day 11 dose for the twice-weekly schedule and a 2-fold accumulation (based on AUC) following the Day 15 dose for the once-weekly schedule.

Mean plasma clearance (CL) of ixazomib is 1.86 L/hr based on the results of a population PK analysis. Taken together with the blood-to-plasma AUC ratio of approximately 10, it can be inferred that ixazomib is a low clearance drug. Using the absolute oral bioavailability (F) estimate of 58% (also from a population PK model), this translates to an apparent oral plasma clearance (CL/F) of 3.21 L/hr. The geometric mean renal clearance for ixazomib is 0.119 L/hr, which is 3.7% of CL/F and 6.4% of CL estimated in a population PK analysis. Therefore, renal

clearance does not meaningfully contribute to ixazomib clearance in humans. Approximately 62% of the administered radioactivity in the ADME study (Study C16016) was recovered in the urine and 22% of the total radioactivity was recovered in the feces after oral administration. Only 3.2% of the administered ixazomib dose was recovered in the urine as unchanged ixazomib up to 168 hours after oral dosing, suggesting that most of the total radioactivity in urine was attributable to metabolites.

The PK of ixazomib was similar with and without co-administration of clarithromycin, a strong CYP3A inhibitor, and hence no dose adjustment is necessary when ixazomib is administered with strong CYP3A inhibitors. Consistently, in a population PK analysis, co-administration of strong CYP1A2 inhibitors did not affect ixazomib clearance. Therefore, no dose adjustment is required for patients receiving strong inhibitors of CYP1A2. Based on information from the clinical rifampin DDI study, ixazomib C_{max} and $AUC_{0\text{-last}}$ were reduced in the presence of rifampin by approximately 54% and 74%, respectively. Therefore, the co-administration of strong CYP3A inducers with ixazomib is not recommended.

Mild or moderate renal impairment (CrCL ≥ 30 mL/min) did not alter the PK of ixazomib based on the results from a population PK analysis. As a result, no dose adjustment is required for patients with mild or moderate renal impairment. In a dedicated renal impairment study (C16015), unbound $AUC_{0\text{-last}}$ was 38% higher in patients with severe renal impairment or ESRD patients requiring dialysis as compared to patients with normal renal function. Accordingly, a reduced starting dose of ixazomib is appropriate in patients with severe renal impairment or ESRD requiring dialysis. Pre- and post-dialyzer concentrations of ixazomib measured during the hemodialysis session were similar, suggesting that ixazomib is not readily dialyzable, consistent with its high plasma protein binding (99%).

The PK of ixazomib is similar in patients with normal hepatic function and in patients with mild hepatic impairment, as defined by the National Cancer Institute Organ Dysfunction Working Group (total bilirubin <1.5 times the upper limit of normal [ULN]), based on the results from a population PK analysis. Consequently, no dose adjustment is required for patients with mild hepatic impairment. In a dedicated PK study in patients with moderate (total bilirubin >1.5 to 3 times the ULN) or severe (total bilirubin >3 times the ULN) hepatic impairment (Study C16018), unbound dose-normalized $AUC_{0\text{-last}}$ was 27% higher in patients with moderate or severe hepatic impairment as compared to patients with normal hepatic function. Therefore, a reduced starting dose of ixazomib is appropriate in patients with moderate or severe hepatic impairment.

There was no statistically significant effect of age (23-91 years), sex, body surface area (1.2-2.7 m^2), or race on the clearance of ixazomib based on the results from a population PK analysis.

Further details on these studies are provided in the IB.

1.5 Clinical Trial Experience Using the Oral Formulation of Ixazomib

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

1.6 Relapsed and/or Refractory Multiple Myeloma

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

1.7 Newly Diagnosed Multiple Myeloma (NDMM)

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

1.8 Clinical Trial Experience Using the Intravenous Formulation of Ixazomib

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

1.9 Study Rationale

Therapy for Mantle cell lymphoma has evolved rapidly over the past decade. Ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor has set a new standard for relapsed MCL, with many ongoing studies for frontline utilization. However, patients who are refractory of ibrutinib face a difficult therapeutic challenge and poor survival outcome. One pathway believed to have significant role in ibrutinib refractoriness is over activation of the NFKB pathway. Proteasome inhibition has been a successful therapeutic intervention in relapsed MCL. However, the delivery logistics and side effects of proteasome inhibition have been difficult to manage and hence been underutilized. Therefore, ixazomib with its oral delivery system and milder side

effect profile would represent an improved modality for single and combination studies in this ibrutinib refractory MCL population.

Rituximab is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen expressed on the surface of normal and malignant B lymphocytes. Rituximab is approved by the US Food and Drug Administration (FDA) for the treatment of patients with low grade CD20+ B-cell NHL. Rituximab kills NHL cells by multiple mechanisms, including direct induction of apoptosis, and by stimulating antibody-dependent cellular cytotoxicity (ADCC) and complement-mediated cytotoxicity.

A retrospective analysis was performed to delineate the role of rituximab in the treatment of mantle cell lymphoma. Patients with newly-diagnosed MCL (n=37) and previously-treated MCL (n=50) received single-agent rituximab in the context of two multicenter clinical studies in 1996 and 1997. The overall response rate was 37% (30 of 81 evaluable patients). The complete response rate was 14%. There was no difference in response rates between newly-diagnosed and previously-treated patients. At a median follow-up of 1.4 years, the median time to disease progression was 7 months. The median duration of response was one year, and was significantly longer for patients achieving CR vs. PR (p=0.04).

1.10 Potential Risks and Benefits

Please refer to the current ixazomib IB.

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.

Proteasome inhibitor in combination with rituximab has been studied mantle cell lymphoma and other NHL without. The combination studies of proteasome inhibitor and rituximab did not accentuate toxicity.

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

2. STUDY OBJECTIVES

2.1 Primary Objectives

- To evaluate the complete remission rate of BTK inhibitor refractory MCL patients with ixazomib and rituximab at 16 weeks of therapy.

2.2 Secondary Objectives

1. To evaluate overall response rate (ORR) assessed by Lugano Criteria (2014). ORR is the summation of partial remission + complete remission rates.

- To evaluate progression free survival (PFS) and overall survival (OS). Progression free survival time is the time interval from the start date of treatment to the date of progression or death due to any cause whichever happened first. Overall survival time is the time interval from the start date of treatment to death date. Patients will be censored at the last follow-up date if progression or death didn't occur.
- To evaluate the safety and tolerability

2.3 Tertiary/Exploratory Objectives

To evaluate biomarkers of response to treatment and mechanisms of resistance with pretreatment and post-treatment bone marrow and blood samples with DNA and RNA sequencing and immune profiling by flow cytometry

3. STUDY ENDPOINTS

3.1 Primary Endpoints

Complete remission rate of BTK inhibitor refractory MCL patients with ixazomib and rituximab at 16 weeks of therapy.

3.2 Secondary Endpoints

ORR as assessed by Lugano criteria (2014) at 16 weeks, TTR, PFS and OS

Safety and tolerability at completion at weeks 8, 16, 28, 42 and 56 weeks. Toxicities will/ be measured using CTCAE v4.0.

3.3 Tertiary/Exploratory Endpoints

Biomarkers of response to treatment and mechanisms of resistance with pretreatment and post-treatment bone marrow and blood samples with DNA and RNA sequencing and immune profiling by flow cytometry.

4. STUDY DESIGN

4.1 Overview of Study Design

Open label, single center, single –arm, phase II testing the combination of ixazomib and rituximab in the treatment of subjects with relapsed or refractory MCL. The study will enroll 24 patients. The treatment plan starts with oral ixazomib at the US approved dose of 4 mg. All subjects will have disease restaging at 8 weeks. Rituximab IV will be given once weekly for the first 4 weeks. Rituximab IV will restart at cycle 3, and continue monthly until cycle 12.

4.2 Number of Patients

Twenty four subjects will be anticipated.

4.3 Duration of Study

The study will recruit patients at a rate of 2 patients per month. Anticipate 2 year recruitment unless futility endpoint is met and the study will terminate if futility conditions are met. We will have approximately one year follow up from the last patient enrolled. Anticipate 3 years duration of study.

5. STUDY POPULATION

5.1 Inclusion Criteria

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

1. Male or female patients 18 years or older.

2. Patients must have histologically confirmed diagnosis of Mantle Cell Lymphoma.

3. Patients must have measurable disease, as defined by at least one of the following:

   - Lymph node or mass 2 cm or greater, splenomegaly > 13 cm
   - Bone marrow only disease as per morphology or flow cytometry

4. Patients must have relapsed and/or refractory disease to at least 2 lines of therapy including either an anthracyline- or bendamustine- based regimen and a BTK inhibitor.

5. Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status and/or other performance status 0, 1, or 2.

6. Patients must have normal organ and marrow function as defined below:

   a. Absolute neutrophil count (ANC) $\geq 1{,}000/mm^3$
   b. Platelets $\geq 50{,}000/mm^3$
   c. Total bilirubin $< 1.5 \times$ institutional upper limit of normal (ULN). In patients with documented Gilbert's syndrome, total bilirubin $\leq 2.5 \times$ ULN.
   d. AST (SGOT)/ALT(SGPT) $\leq 3 \times$ ULN
   e. Creatinine clearance ≥ 30 mL/min (See Appendix 11.2)

7. Patients must be willing to give written consent before performance of any study related procedures not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

8. Female patients who:

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

9. Male patients, even if surgically sterilized (i.e., 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 patient. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

5.2 Exclusion Criteria

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

1. Female patients who are lactating or have a positive serum pregnancy test during the screening period.
2. Failure to have fully recovered (i.e., ≤ Grade 1 toxicity) from the reversible effects of prior chemotherapy.
3. Major surgery within 14 days before enrollment.

4. Radiotherapy within 14 days before enrollment. If the involved field is small, 7 days will be considered a sufficient interval between treatment and administration of the ixazomib.

5. Central nervous system involvement.

6. Infection requiring systemic antibiotic therapy or other serious infection within 14 days before study enrollment. Patient may be eligible, if infectious disease specialist approves start of therapy AND subject has completed course of antibiotic therapy.

7. 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.

8. Systemic treatment, within 14 days before the first dose of ixazomib, with strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of St. John's wort.

9. Ongoing or active systemic infection, active (DNA PCR positivity) hepatitis B or C virus infection, or known human immunodeficiency virus (HIV) positive.

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

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

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

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

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

15. 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.

16. Patients that have previously been treated with proteasome inhibitors, or participated in a study with proteasome inhibitors whether treated with proteasome inhibitors or not.

6. STUDY DRUG

6.1 Description of Investigational Agents

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

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

For additional details, please see the ixazomib IB.

6.2 Study Drug Administration

Cycles 1-12 (28-day cycle)

- Ixazomib 4 mg PO on Days 1, 8, and 15 (3 mg if CrCl < 30 mL/min)
- Rituximab 375mg/m^2 IV weekly for the first 4 weeks in cycle 1, and starting cycle 3, Rituximab 375mg/m^2 IV will be given on Day 1 of each cycle. Total of 12 cycles will be given.

Patients benefiting from the clinical trial will continue with Ixazomib indefinitely until patient withdraws consent, disease progression or unacceptable toxicity.

Ixazomib Administration

All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). Patients should be monitored for toxicity, as necessary, and doses of ixazomib should be modified as

needed to accommodate patient tolerance to treatment; this may include symptomatic treatment, dose interruptions, and adjustments of ixazomib dose (see Section 6.3).

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

The prescribed administration of ixazomib doses in this study is 4 mg ixazomib in a 28 day cycle.

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

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

Ixazomib Destruction

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

Rituximab Administration

Pre-medication consisting of acetaminophen and diphenhydramine should be considered before each infusion of rituximab to attenuate potential infusion reactions. Since transient hypotension may occur during rituximab infusion, consideration should be given to withholding antihypertensive medications 12 hours prior to rituximab infusion.

Rituximab First Infusion*: 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 to 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. If hypersensitivity or an

infusion- related event develops, the infusion should be temporarily slowed or interrupted. The infusion can continue at one-half the previous rate upon improvement of patient symptoms.

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 30 minute intervals, to a maximum of 400 mg/hr as tolerated.

*Patients with peripheral blood involvement (leukemic presentation) as defined for this purpose as > 20,000 lymphocytes per mm3 as determined by flow cytometry studies, rituximab will NOT be initiated on Day 1. In this case, ixazomib will be started alone. Rituximab may be initiated on the next cycle if the lymphocyte count drops to < 20,000/mm3 in peripheral blood. For such patients, or for those with high tumor burden, despite lymphocyte count < 20,000 cells/mm3 (as determined by the principal investigator), infusion of rituximab may be abbreviated as outlined below. If the patient progresses despite one cycle of ixazomib, the patient will be taken off protocol.

Day 1 – Rituximab 50 mg/m2

Day 2 – If no cytokine release phenomenon is noted on Day 1 and the peripheral blood white cell counts have decreased to < 20,000 cells/mm3 or < 25% of base line WBC counts, then the dose of rituximab can be increased to 325 mg/m2 on Day 2 at PI discretion.
A similar 2-day split dose approach may be taken for rituximab infusion on Days 8, 15 and 22 in patients with high tumor burden or high peripheral blood WBC counts as determined by the PI prior to each infusion of rituximab. If initiation of rituximab is delayed until Cycle 2, it will be followed by rituximab on day one of every cycle starting in Cycles 4 – 8.
Please refer to rituximab package insert for details concerning drug storage, preparation and administration guidelines.

All rituximab infusions will be administered at MD Anderson.

6.3 Risk for TLS

6.3.1 High Risk for TLS:

High risk for TLS – Subjects with high tumor burden (at least one lesion >10 cm; or at least one lesion >5 cm and lymphocyte count >25,000 cells/mm^3) and/or with baseline creatinine clearance (CrCl) <80 mL/min.

- Subjects at high risk for TLS will be hospitalized for a minimum of 24 hours (and up to 48 hours at the discretion of the investigator) after the first dose of ixazomib for monitoring and prophylaxis of TLS.
- During hospitalization of the first dose for high risk pts, Blood Chemistries should be analyzed at baseline, between 4-8 hours, 12-24 hours after administration of the drug for signs of electrolyte changes. The 24 blood chemistries should be analyzed for signs of TLS prior to administering next dose of ixazomib.
- Patients should receive oral hydration of 1.5 – 2 liters of fluid and 150 – 200 m/hr as tolerated. Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of therapy and rasburicase if baseline uric acid is elevated.
- Pre-dose blood chemistries at each step up dose of ixazomib and correct any blood chemistry abnormalities.
- For high-risk patients, outpatient monitoring should occur at next dose pre-dose, 6-8 hour and 24 hours. The next dose should not be administrated until the 24 hour labs are examined for signs of TLS

6.3.2 Medium Risk for TLS

Any lymph node 5 cm to <10 cm OR lymphocyte count ≥ 25 x109/L

- Patients should receive oral hydration of 1.5 – 2 liters of fluid and start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of therapy and consider additional intravenous fluids.
- Pre-dose blood chemistries at each step up dose of ixazomib and correct any blood chemistry abnormalities.
- Medium risk patients should have outpatient monitoring of blood chemistries for the 1st dose of ixazomib. Monitoring should occur at baseline, 6-8 hours and 24 hours. The next dose should not be administered until the 24 hour lab results are examined for signs of TLS. Subsequent doses require a pre-dose blood chemistry assessment.

6.3.3 Low Risk for TLS

All others not meeting the criteria for high risk for TLS.

- Patients should receive oral hydration of 1.5 – 2 liters of fluid and start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of therapy if uric acid levels are

above normal reference range.

- Pre-dose blood chemistries at each dose of ixazomib and correct any blood chemistry abnormalities.
- Low risk pts should have outpatient monitoring of blood chemistries for the 1st dose of ixazomib. Monitoring should occur at baseline. If abnormal renal function (Cr > 1.4) or above normal randge on uric acid. Should repeat complete metabolic panel (CMP) in 24 hours to make sure no biochemical evidence of tumor lysis.

6.4 Dose-Modification Guidelines

6.4.1 Recommended Ixazomib Criteria for Beginning or Delaying a Subsequent Treatment Cycle & Dose Modifications for Treatment Associated Toxicity

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

- ANC must be ≥ 1,000/mm^3.
- Platelet count must be ≥ 50,000/mm^3.
- All other nonhematologic toxicity (except for alopecia) must have resolved to ≤ Grade 1 or to the patient's baseline condition

If the patient fails to meet the above-cited criteria for initiation of the next cycle of treatment, dosing should be delayed for 1 week. At the end of that time, the patient should be re-evaluated to determine whether the criteria have been met. If the patient continues to fail to meet the above-cited criteria, delay therapy and continue to reevaluate. The maximum delay before treatment should be discontinued will be 3 weeks 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

6.4.2 Dosage in Patients with Renal Impairment

Reduce the starting dose of Ixazomib (MLN908) to 3 mg in patients with severe renal impairment (creatinine clearance less than 30 mL/min) or end-stage renal disease (ESRD) requiring dialysis. Ixazomib is not dialyzable and therefore can be administered without regard to the timing of dialysis

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

Table 6-2 Ixazomib Dose Adjustments for Hematologic Toxicities

Criteria	Action
Within-Cycle Dose Modifications	
• If platelet count ≤ 30×10^9/L or ANC ≤ 0.50×10^9/L on a ixazomib dosing day (other than Day 1)	• Ixazomib dose should be withheld. • Complete blood count (CBC) with differential should be repeated at least every other day until the ANC and/or platelet counts have exceeded the prespecified values (see Section 6.3.1) on at least 2 occasions. • Upon recovery, ixazomib may be reinitiated with 1 dose level reduction.
Dose Modifications for Subsequent Treatment Cycles	
• Delay of > 2 weeks in the start of a subsequent cycle due to lack of toxicity recovery as defined in Section 6.3.1. • ANC < 1.0×10^9/L, platelet count < 50×10^9/L	• Hold ixazomib until resolution as per criteria Section 6.3.1. • Upon recovery, reduce ixazomib 1 dose level. • The maximum delay before treatment should be discontinued will be 3 weeks or at the discretion of the PI.
Dose Modifications for Subsequent Treatment Cycles	
• All hematologic toxicities	• For hematologic toxicity that occurs during a cycle but recover in time for the start of the next cycle,: o If dose was reduced within the cycle, start the next cycle at that same dose. o If due to toxicity timing, i.e., after Day 15 dosing thus a dose reduction was not required at that point in the cycle, reduce ixazomib by 1 dose level at the start of that cycle. o Do not reduce the dose both within a cycle and at the start of the cycle for the same most severe toxicity.

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

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

Adverse Event (Severity)	Action on Study Drug	Further Considerations
Peripheral Neuropathy:		
Grade 1 peripheral neuropathy	• No action	Grade 1 signs and symptoms: asymptomatic; without pain or loss of function; clinical or diagnostic observations only [14]
New or worsening Grade 1 peripheral neuropathy with pain or Grade 2	• Hold study drug until resolution to Grade ≤ 1 or baseline	Grade 2 signs and symptoms: Moderate symptoms; limiting instrumental activities of daily living (ADL) [14]
New or worsening Grade 2 peripheral neuropathy with pain or Grade 3	• Hold study drug until resolution to Grade ≤ 1 or baseline • Reduce study drug to next lower dose upon recovery	Grade 3 signs and symptoms: severe symptoms; limiting self-care ADL; assistive device indicated [14]
New or worsening Grade 4 peripheral neuropathy	• Discontinue study drug	
Grade 2 Rash	• Symptomatic recommendations as per section 6.7	The investigator and project clinician may discuss considerations for dose modifications and symptom management.
Grade 3 nonhematologic toxicity judged to be related to study drug	• Hold study drug until resolution to Grade < 1 or baseline	Symptomatic recommendations noted in Section 6.7

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

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

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

Rituximab and Ixazomib individually are FDA approved for NHL and multiple myeloma, respectively. The combination of a proteasome inhibitor plus anti-CD20 antibody has been studied previously.

Mechanistically, rituximab and Ixazomib does not have over lapping mechanism of action. We have in place Hepatitis screening at baseline. Rituximab does not have overlapping non-hematologic toxicity with Ixazomib. However, they will both cause cytotoxicity to hematopoietic cells, cytopenias and related increased risk for infection. We are mainly concerned for non-hematologic toxicities. Therefore, we would like to monitor peripheral neuropathy toxicities. We will stop the current dose level and consider treating patients at a lower dose level for Ixazomib if we observe at anytime that the rate of any grade of peripheral neuropathy toxicity is > 40% or the rate of grade 3 or higher peripheral neuropathy toxicity is >10%.

6.4.3 Recommended Dose Modifications for Rituximab Treatment Associated Toxicity

There will be no dose reductions for rituximab. However, the rate of infusion may be reduced for patients experiencing hypersensitivity reaction.

Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study.

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 (Rationale: If there were to be a drug-drug interaction with an inducer, ixazomib exposure would be decreased):

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

The following medicinal products and procedures are prohibited during the study.

- Excluded foods and dietary supplements include St. John's wort.
- Any antineoplastic treatment with activity against MCL, other than study drugs
- 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 study drug dosing for any dosing day

6.5 Permitted Concomitant Medications and Procedures

The following medications and procedures are permitted during the study:

- Antiemetics, including 5-HT3 serotonin receptor antagonists, may be used at the discretion of the investigator.
- Loperamide or other antidiarrheal should be used for symptomatic diarrhea at discretion of the investigator. The dose and regimen will be according to institutional guidelines. IVF should be given to prevent volume depletion.
- Growth factors (e.g., granulocyte colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF], recombinant erythropoietin) are permitted. Their use should follow published guidelines and/or institutional practice; however, alternative usage may be reviewed with the Millennium Clinical or Medical Representative . Erythropoietin will be allowed in this study. Their use should follow published guidelines and/or institutional practice.

- Patients should be transfused with red cells and platelets as clinically indicated and according to institutional guidelines.

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

- Concomitant treatment with bisphosphonates will be permitted, as appropriate.

- Patients who experience worsening neuropathy from baseline may be observed for recovery, and have dose reductions/delays as indicated in the protocol, and any supportive therapy or intervention may be initiated as appropriate at the discretion of the investigator.

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

6.6 Precautions and Restrictions

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

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

Pregnancy

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

Female patients must meet 1 of the following:

- 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 [e.g., calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)

Male patients, even if surgically sterilized (i.e., 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 [e.g., calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)

6.7 Management of Clinical Events

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

Prophylaxis Against Risk of Reactivation of Herpes Infection

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

Nausea and/or Vomiting

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

Diarrhea

Prophylactic antidiarrheals will not be used in this protocol. However, diarrhea should be managed according to clinical practice, including the administration of antidiarrheals once

infectious causes are excluded. Fluid intake should be maintained to avoid dehydration. Fluid deficit should be corrected before initiation of treatment and during treatment.

Erythematous Rash With or Without Pruritus

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

Symptomatic measures such as antihistamines or corticosteroids (oral or topical) have been successfully used to manage rash and have been used prophylactically in subsequent cycles. The use of a topical, IV, or oral steroid (e.g., 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 (e.g., using a thick, alcohol-free emollient cream on dry areas of the body or oral or topical antihistamines). A rare risk is Stevens-Johnson Syndrome, a severe and potentially life-threatening rash with skin peeling and mouth sores, which should be managed symptomatically according to standard medical practice. Punch biopsies for histopathological analysis are encouraged at the discretion of the investigator.

Thrombocytopenia

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

characterized by thrombocytopenia, petechiae, fever, or possibly more serious signs and symptoms. TTP should be managed symptomatically according to standard medical practice.

Neutropenia

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

Fluid Deficit

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

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

Hypotension

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

Posterior Reversible Encephalopathy Syndrome

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

Transverse Myelitis

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

6.8 Preparation, Reconstitution, and Dispensing

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

Rituximab

Use appropriate aseptic technique. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Rituximab should be a clear, colorless liquid. Do not use vial if particulates or discoloration is present. Administration Withdraw the necessary amount of rituximab and dilute to a final concentration of 1 mg/mL to 4 mg/mL in an infusion bag containing either 0.9% Sodium Chloride, USP, or 5% Dextrose in Water, USP. Gently invert the bag to mix the solution. Do not mix or dilute with other drugs. Discard any unused portion left in the vial. Storage rituximab solutions for infusion may be stored at 2°C–8°C (36°F–46°F) for 24 hours. rituximab solutions for infusion have been shown to be stable for an additional 24 hours at room temperature. However, since rituximab solutions do not contain a preservative, diluted solutions should be stored refrigerated (2°C–8°C). No incompatibilities between rituximab and polyvinylchloride or polyethylene bags have been observed.

6.9 Packaging and Labeling

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

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

6.10 Storage, Handling, and Accountability

Upon receipt at the investigative site, ixazomib should remain in the blister and carton provided until use or until drug is dispensed. The container should be stored at the investigative site as per

labeled instructions (do not store above 30ºC or 86°F, do not freeze). 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 stored per labeled instructions 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 per labeled instructions (not store above 30ºC or 86°F, do not freeze) 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.

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

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

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

6.11 Study Compliance

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

6.12 Treatment Assignment *(if applicable)*

Open labeled single armed study, all subjects will receive study medications of ixazomib and rituximab dispensed from MD Anderson Institutional pharmacy.

6.13 Termination of Treatment and/or Study Participation

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

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

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

7. STATISTICAL AND QUANTITATIVE ANALYSES

7.1 Statistical Methods

Primary endpoint: complete response rate at 16 weeks measured using Lugano (2014)

Patient populations

All endpoints will be measured on patients that received at least one dose of the study drug.

7.1.1 Determination of Sample Size

We plan to enroll 24 patients. When the true complete response rate at 4 months (week 16) is 30%, a cohort size of 24 subjects will provide a 95% confidence interval with a lower bound of 0.12 which is higher than the CR rate of 10% observed historically for Rituximab monotherapy.

7.1.2 Randomization and Stratification

No patient will be randomized.

7.1.3 Populations for Analysis

Primary endpoint:

1. Complete remission rate of BTK inhibitor refractory MCL patients with ixazomib and rituximab at 16 weeks of therapy.

Secondary endpoints:

1. ORR using Lugano Criterion at 16 weeks. ORR is the summation of partial remission + complete remission rates.
2. PFS and OS is defined as the time from commencement of treatment to the date of progression and death from any cause, respectively. Progression free survival time is the time interval from the start date of treatment to the date of progression or death due to any cause whichever happened first. Overall survival time is the time interval from the start date of treatment to death date. Patients will be censored at the last follow-up date if progression or death didn't occur.
3. Tolerability: completion at weeks 8, 16, 28, 42 and 56. Toxicity measured using CTCAE V4.0.

7.1.4 Procedures for Handling Missing, Unused, and Spurious Data

There will be no missing, unused or spurious data.

7.1.5 Demographic and Baseline Characteristics

Clinical and laboratory characteristics, age, sex, stage, MIPI scores etc., will be scored and presented in tabular or percentage form.

7.1.6 Efficacy Analysis

Overall response and complete response at each of the pre-specified time points will be described as percentage with exact ninety-five percent (95%) confidence interval based on binomial distribution. PFS and OS curves will be described using Kaplan-Meier methods. The curves will be presented with 95% confidence intervals. Patients who are still on follow-up without experiencing the relevant event by the closeout date will be censored. The maximum grade of each toxicity will be described in tabular form as count and percentages.

7.1.7 Pharmacokinetics/Pharmacodynamics/Biomarkers

Patient immunity and MCL profile: Alterations in patient immune parameters and MCL profile during various (screening, end of cycle 4, end of cycle 8, end of cycle 15, and end of study) time points during therapy will be assessed by 8 colored flow cytometry, evaluating populations of T cell, regulatory T cells, PD-1 and PDL1 expressions to generate hypothesis for future studies in combination with checkpoint inhibitors or Bispecific antibody therapies. Blood and bone marrow samples will be collected under protocol LAB11-0342 (*Collection and use of samples from patients with lymphoma, multiple myeloma, and other plasma cell dyscrasias for translational research,* PI: Liang Zhang) and transported to specified laboratory. Participants will sign a separate consent for their samples to be collected under LAB11-0342.

Minimal residual disease (MRD) measurement by Flow Cytometry: a four color assay as per institutional pathology flow cytometry analysis, CD3, CD4, CD5, CD8, CD10, CD19, CDCD20 CD22, CD34, CD38, CD43, CD45 CD56, CD200 and Lambda and Kappa. Blood and bone marrow samples will be collected under protocol LAB11-0342 (*Collection and use of samples from patients with lymphoma, multiple myeloma, and other plasma cell dyscrasias for translational research,* PI: Liang Zhang) and transported to specified laboratory. Participants will sign a separate consent for their samples to be collected under LAB11-0342.

7.1.8 Safety Analysis

Adverse event monitoring, vital signs, physical examination, 12-lead ECG, and laboratory assessments will be evaluated. Guidelines for the management for TLS are provided below in

Section 7.1.8.1. A safety analysis will be performed for all subjects participating in the study who took at least 1 dose of study drug.

For patient safety, the event of grade 3 or higher peripheral neuropathy toxicity within the first two cycles will be monitored. A rate of higher than 20% is considered excessive.

The prior probability of grade 3 or higher peripheral neuropathy toxicity is modelled by beta distribution (Beta (0.2, 0.8)). Denoting the probability of toxicity by p (TOX), the following decision criterion will be applied: We will stop the current dose level and consider treating patients at a lower dose level for Ixazomib if Prob{p(TOX) > 20% | data} > 0.90

Patients will be monitored in a cohort of 6 according to the following stopping boundaries for grade 3 or higher peripheral neuropathy toxicity.

Number of patients evaluated	Recommend stopping if ≥ toxicities observed
6	3-6
12	5-12
18	7-18
24	Always stop with this many patients

The operating characteristics are summarized in the following table (based on simulations from 10,000 trials).

True Toxicity Rate	Prob(stop the dose early)	Average number of patients treated
0.05	0.0023	23.96
0.10	0.0182	23.69
0.15	0.0616	23.00
0.20	0.1439	21.76

0.25	0.2677	19.97
0.30	0.4214	17.77
0.35	0.5831	15.39

7.1.8.1 Recommendation for Management of Tumor Lysis Syndrome (TLS)

Event	Occurrence	Action
Tumor Lysis Syndrome		
Blood chemistry changes or symptoms suggestive of TLS	Any	Withhold the next dose. If resolved within 24 to 48 hours of last dose, resume at the same dose.
		For any blood chemistry changes requiring more than 48 hours to resolve, resume at a reduced dose by one dose level.
		For any events of clinical TLS, resume at a reduced dose following resolution.

7.1.9 Interim Analysis

If early progression occurs in 2 or more of the first 5 patients, or 4 or more of the first 10 patientsprior to the first restaging at week 16, the study will be closed for future enrollment. Using this rule, the probability of stopping the study early is 81.3% after 5 patients and 89.6% after 10 patients when the true rate of early progression is 50%. Early progression is defined as greater than 50% increase in the sum of bidirectional tumor measurement or new lesion prior to the first restaging at week 16.

8. ADVERSE EVENTS

8.1 Definitions

8.1.1 Adverse Event Definition

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

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.
The investigator (or physician designee) is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for all adverse events for subjects enrolled.

For the purposes of this clinical study, AEs include events which are either new or represent detectable exacerbations of pre-existing conditions.

The term “disease progression” should not be reported as an adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition. As an example, "worsening of underlying disease" or the clinical diagnosis that is associated with disease progression should be reported.

Adverse events may include, but are not limited to:

- Subjective or objective symptoms provided by the patient and/or observed by the Investigator or study staff including laboratory abnormalities of clinical significance.
- Any AEs experienced by the patient from the time of informed consent through the completion of final study procedures (approximately 30 days following the last dose of study drug).
- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with the underlying disease that were not present before the AE reporting period

- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as biopsies).

The following are NOT considered AEs:

- Pre-existing condition: A pre-existing condition (documented on the medical history CRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.
- Pre-planned or elective hospitalization: A hospitalization planned before signing the informed consent form is not considered an SAE, but rather a therapeutic intervention. However, if during the pre-planned hospitalization an event occurs, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration, but not performed before enrollment in the study, will not be considered serious if they are performed after enrollment in the study for a condition that has not changed from its baseline level. Elective hospitalizations for social reasons, solely for the administration of chemotherapy, or due to long travel distances are also not SAEs.
- Diagnostic testing and procedures: Testing and procedures should not to be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported.
- Asymptomatic treatment related lymphocytosis: This event should also not be considered an AE. Patients with treatment-related lymphocytosis should remain on study treatment and continue with all study-related procedures.

Recommended Adverse Event Recording Guidelines

Attribution	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

8.1.2 Adverse Drug Reaction

An adverse drug reaction (ADR) is a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. This includes adverse reactions which arise from: use of a medicinal product within the terms of the marketing authorization; use outside the terms of the marketing authorization, including overdose, misuse, abuse and medication errors; and occupational exposure*.

* This corresponds to the exposure to a medicinal product for human use as a result of one's occupation, such as nurses who may handle products routinely in their occupational setting.

8.1.3 Serious Adverse Event Definition

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

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

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

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

8.2 Procedures for Reporting Serious Adverse Events

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.

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 dose 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). Active follow up for detection of second primary malignancies beyond the planned study is not required; however, if the sponsor-investigator learns about the occurrence of a second primary malignancy in one of the study patients within 3 years after the last study drug administration he must report the event 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).

The principal investigator, Hun Ju Lee 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 in English to Millennium Pharmacovigilance (or designee):

> **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

US & Canada
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

- Any other form deemed appropriate by the sponsor-investigator

8.3 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.

Suggested Pregnancy Reporting Form:

- Pregnancy Report Form (provided by Millennium)

9. ADMINISTRATIVE REQUIREMENTS

9.1 Data Collection

Data for the study will be collected and entered in RedCap database and in CORe.

9.2 Data Confidentiality Plan

To maintain patient confidentiality, all information will be de-identified and only labeled with a sponsor provided deidentifed random number key. A confidential list will be created that links the code to the subject's name. However, patient confidentiality will be strictly maintained at all times. Only authorized people (PI, delegated research staff) will have access to the list of names. The data and the confidential list of coded names will be kept securely at MD Anderson / Red Cap database and password protected behind the institutional firewall. This information is expected to lead to publication and confidentiality will be maintained throughout the analysis. No individual patient will be identified in any published or presented data, only summary data will be used. All paper files containing data will be destroyed per MDACC policy on medical records retention and destruction within 5 years after study publication. Electronic data will not be destroyed after 5 years as electronic data on MDACC servers is stored indefinitely.

9.3 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 Millennium (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.

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. While overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Investigators must record all medication errors (including overdose) on the appropriate CRF form. Individuals who identify a potential medication error situation should immediately contact Takeda (see below) and report the event.

For Product Complaints, or Medication Errors (Including Overdose), contact Takeda Pharmacovigilance
Phone: 1-844-N1-POINT (1-844-617-6468)
E-mail: GlobalOncologyMedinfo@takeda.com
Fax: 1-800-881-6092
Hours: Mon-Fri, 9 a.m. – 7 p.m. ET

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).

10. REFERENCES

1. Cheson, B., et al., *Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification.* Journal of Clinical Oncology 2014 32:27, 3059-3067
2. Gupta, N., et al., *Clinical Pharmacokinetics of Intravenous and Oral MLN9708, An Investigational Proteasome Inhibitor: An Analysis of Data From Four Phase 1 Monotherapy Studies.* in *52nd ASH Annual Meeting and Exposition*, 2010. **116**(21): p. abstr 1813.
3. Gupta, N., M. Saleh, and K. Venkatakrishnan. *Flat-Dosing Versus BSA-Based Dosing for MLN9708, An Investigational Proteasome Inhibitor: Population Pharmacokinetic (PK) Analysis of Pooled Data From 4 Phase-1 Studies* in *53rd ASH Annual Meeting and Exposition*. 2011. San Diego, CA; p. abstr 1433
4. Chow, L.Q., et al. *MLN9708, an investigational proteasome inhibitor, in patients with solid tumors; Updated phase 1 results* in *Head and Neck Symposium*. 2012. Phoenix, AZ
5. Assouline, S., et al. *Once-weekly MLN9708, an investigational proteasome inhibitor, in patients with relapsed/refractory lymphoma: results of a phase 1 dose-escalation study* in *17th EHA Annual Congress.* 2012. Amsterdam, the Netherlands.
6. Lonial, S., et al. *Phase I study of twice-weekly dosing of the investigational oral proteasome inhibitor MLN9708 in patients (pts) with relapsed and/or refractory multiple myeloma (MM)* in *ASCO Annual Meeting*. 2012. Chicago, Illinois.
7. Kumar S, et al. *Weekly Dosing of the Investigational Oral Proteasome Inhibitor MLN9708 in Patients with Relapsed and/or Refractory Multiple Myeloma: Results From a Phase 1 Dose-Escalation Study* In *53rd ASH Annual Meeting and Exposition*; 2011 10-13 Dec; San Diego, CA; p. abstr 816..
8. Merlini, G., et al. *MLN9708, a Novel, Investigational Oral Proteasome Inhibitor, in Patients with Relapsed or Refractory Light-Chain Amyloidosis (AL): Results of a Phase 1 Study* in *54th ASH Annual Meeting and Exposition*. 2012. Atlanta, Georgia.
9. Kumar, S. et al. *A Phase 1/2 Study of Weekly MLN9708, an Investigational Oral Proteasome Inhibitor, in Combination with Lenalidomide and Dexamethasone in Patients with Previously Untreated Multiple Myeloma (MM)* in *54th ASH Annual Meeting and Exposition*. 2012. Atlanta, Georgia.
10. Richardson, P.G., et al. *MLN9708, an investigational proteasome inhibitor, in combination with lenalidomide and dexamethasone in previously untreated multiple myeloma patients (pts): Evaluation of weekly and twice-weekly dosing* in *17th EHA Annual Congress.* 2012. Amsterdam, the Netherlands.
11. San Miguel, J., et al. *Oral MLN9708, an an investigational proteasome inhibitor, in combination with melphalan and prednisone in patients with previously untreated multiple myeloma: a phase 1 study* in *17th EHA Annual Congress.* 2012. Amsterdam, the Netherlands.
12. Richardson P, Baz R, Wang L, Jakubowiak A, Berg D, Liu G, et al. *Investigational Agent MLN9708, An Oral Proteasome Inhibitor, in Patients (Pts) with Relapsed and/or Refractory Multiple Myeloma (MM): Results From the Expansion Cohorts of a Phase 1 Dose-Escalation Study* In: *53rd ASH Annual Meeting and Exposition*; 2011 10-13 Dec; San Diego, CA; p. abstr 301.

13. Lonial S, Baz R, Wang M, Talpaz M, Liu G, Berg D, et al. *Phase I study of twice weekly dosing of the investigational oral proteasome inhibitor MLN9708 in patients (pts) with relapsed and/or refractory multiple myeloma (MM).* J Clin Oncol (ASCO Meeting Abstracts) 2012;30(15 suppl):abstr 8017.
14. Kumar S, Bensinger W, Reeder C, Zimmerman T, Berenson J, Berg D, et al. *Weekly Dosing of the Investigational Oral Proteasome Inhibitor MLN9708 in Patients with Relapsed and/or Refractory Multiple Myeloma: Results From a Phase 1 Dose- Escalation Study* In: *53rd ASH Annual Meeting and Exposition*; 2011 10-13 Dec; San Diego, CA; p. abstr 816.
15. Kumar S, Bensinger W, Reeder C, Zimmerman T, Berenson J, Liu G, et al. *Weekly dosing of the investigational oral proteasome inhibitor MLN9708 in patients (pts) with relapsed/refractory multiple myeloma (MM): A phase I study*. Journal of Clinical Oncology 2012 ASCO Annual Meeting Proceedings 2012:Abstract 8034.
16. Kumar S, Niesvizky R, Berdeja J, Bensinger W, Zimmerman T, Berenson J, et al. Safety and P*harmacokinetics of Weekly MLN9708, an Investigational Oral Proteasome Inhibitor, Alone and in Combination*. Clinical Lymphoma Myeloma and Leukemia 2013;13(Supplement 1):S154; abstr P-230
17. *Common Terminology Criteria for Adverse Events (CTCAE)*. 2010.
18. Lee HJ, Romaguera JE, Feng L, Desai AP, Zhang L, Fanale M, et al. *Phase II Study of Bortezomib in Combination with Cyclophosphamide and Rituximab for Relapsed or Refractory Mantle Cell Lymphoma.* Oncologist. 2017 May;22(5):549-553. doi: 10.1634/theoncologist.2016-0328. Epub 2017 Apr 13.
19. Sonbol MB, Hilal T, Dueck AC, Rosenthal AC, Conley CR, Kosiorek HE, et al. *A phase 2 study of rituximab, cyclophosphamide, bortezomib and dexamethasone (R-CyBorD) in relapsed low grade and mantle cell lymphoma*, Leukemia & Lymphoma, 59:9, 2128-2134, DOI: 10.1080/10428194.2017.1416368

11. APPENDICES

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

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

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

11.2 Cockcroft-Gault Equation

For males:

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

For females:

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

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

==

11.3 SCHEDULE OF STUDY ASSESSMENTS

Days (+/-3d)	Screening[A]	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	C7D1	C8D1	C9D1	C10D1	C11D1	C12D1	C13D1	C14D1	C15D1+	EOS (+/- 7 days)
Informed consent, review inclusion /exclusion, general medical history[B]	X																
Vital signs, weight and height	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG and B symptoms[C]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam[D]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12 lead ECG and ECHO[E]	X																
PET/CT or CT scan[F]	X				X[F]				X[F]				X[F]			X[F]	X[F]
Bone marrow biopsy/aspirate[G]	X				X[G]				X[G]							X[G]	X
MRD assessment[H]	X				X[H]				X[H]							X[H]	X
Tumor biopsy	X																X
CBC, CMP, and Hepatitis Testing [i, j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[J]

Days (+/-3d)	Screening[A]	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	C7D1	C8D1	C9D1	C10D1	C11D1	C12D1	C13D1	C14D1	C15D1	
Quantitative Immunoglobulins	X																
Pregnancy Test	X																

Footnotes Table of Assessments

A. Perform within 28 days prior to cycle 1 day 1. Asssessments performed as standard of care may be used for screening. *BIOPSY TISSUES* obtained up to 8 weeks prior to start of C1D1 can be used as long as we have enough tissue for analysis.

B. Written informed consent form(s) must be signed by the patient before any study specific procedures are performed.

C. B symptoms: Unexplained weight loss>10% over previous 6 months, fever (>38C) and/or drenching night sweats.

D. Complete physical exam at screening, including cardiovascular, respiratory, abdominal, lymph node, skin ENT, extremties and endocrinological examination. Targeted physical exams at subsequent visits, limited to systems of clinical relevance, (i.e., cardiovascular, respiratory, lymph nodes, liver, and spleen), and dose systems associated with clinical signs/symptoms.

E. Single 12-lead ECG and Echo is required at screening. If clinically significant abnormality is noted by the attending physician, a referral to cardiology will be made.

F. CT scans must include neck, chest, abdomen, pelvis and include oral and IV contrast. PET/CT performed at screening, at the end of Cycle 4, at the end of cycle 8, at the end of Cycle 15, and at the End of Study visit if not performed within the last 2 months. After Cycle 15, CT scans will be performed every 4 months. If PET/CT is performed and includes a CT scan of sufficient diagnostic quality and provides bidimensional nodal and liver and spleen measurements, an additional dedicated CT is not required at the time point. MRI may be used in place of CT at investigator's discretion.

G. Bone marrow biopsies/aspirates at specified time points are mandatory (Screening, at the end of cycle 4, at the end of cycle 8, at the end of Cycle 15, and at the End of Study visit) unless shown to be clear on previous examination by multi flow cytometry minimum sensitivity 10-4. * If patient has progression on the study, we do require Bone marrow biopsy/aspiration at progression. For example, if week 9 imaging study shows clear progression beyond a reasonable doubt, we would like to perform a bone marrow biopsy/aspiration for end of study.

H. Minimal residual disease assessment by ASO PCR in mantle cell lymphoma patients and flow cytometry. Peripheral blood will be collected from all patients as well as bone marrow aspirates in those patients required to undergo bone marrow aspirate and biopsy will be collected at Screening, at the end of cycle 4, at the end of cycle 8, at the end of cycle 15, and at the End of Study visit. Collect 20 mL's of blood in EDTA and 5 mL of a bone marrow aspirate in EDTA. Transport within 4 hours at room temperature to appropriate laboratory.

I. Blood chemistry: Sodium, potassium, chloride, BUN, creatinine, glucose, calcium, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin, LDH, phosphate, uric acid, magnesium and bicarbonate.

J. Hepatitis C antibody, hepatitis B surface antigen and hepatitis B core antibody will be evaluated. If hepatitis B core antibody or hepatitis B surface antigen or Hepatitis C antibody is positive, then PCR to quantitate hepatitis B DNA or hepatitis C RNA must be performed. DNA PCR needs to be confirmed negative (<29 U) prior to enrollment in subjects who are hepatitis B core antibody or hepatitis B surface antigen positive. For subjects who are hepatitis C antibody positive, hepatitis C PCR needs to be confirmed negative prior to enrollment. Hepatitis testing does not need to be repeated at the End of Study visit.

Special Attention

Patients who wish to continue with ixazomib after completion of week 56 can continue on with therapy with ixazomib single agent. Rituximab will not be continued post week 56.

End of study biopsy and MRD testing is required.

Medications	C1D1	C1D8	C1D15	C1D21	C2 and Beyond
Rituximab	X	X	X	X	Rituxan to continue C3D1, with each cycle D1
Ixazomib	X	X	X		Continue days 1, 8 and 15 of each cycle.
TLS Assessment[A]	X	X	X	X	Continue days 1, 8 and 15 of each cycle.
Physical Exam	X				
CBC	X	X	X	X	
CMP	X	X	X	X	

A. Patients should be assessed for risk and should receive appropriate prophylaxis for TLS, including hydration and anti-hyperuricemics. Monitor blood chemistries and manage abnormalities promptly. Interrupt dosing if needed. Employ more intensive measures (intravenous hydration, frequent monitoring, hospitalization) as overall risk increases

11.4 Lugano Criteria 2014

Table 2. Revised Staging System for Primary Nodal Lymphomas

Stage	Involvement	Extranodal (E) Status
Limited		
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky*	II as above with "bulky" disease	Not applicable
Advanced		
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

NOTE. Extent of disease is determined by positron emission tomography–computed tomography for avid lymphomas and computed tomography for nonavid histologies. Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.

*Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.

Table 3. Revised Criteria for Response Assessment

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

(continued on following page)

Table 3. Revised Criteria for Response Assessment (continued)

Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Source: *Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification*
Bruce D. Cheson, Richard I. Fisher, Sally F. Barrington, Franco Cavalli, Lawrence H. Schwartz, Emanuele Zucca, and T. Andrew Lister
Journal of Clinical Oncology 2014 32:27, 3059-3067