Official Title:	A Window Study of Ixazomib in Untreated Indolent B-NHL
NCT Number:	NCT02339922
Document Type:	Study Protocol and Statistical Analysis Plan
Date of the Document:	December 27th, 2023

A Window Study of Ixazomib in Untreated Indolent B-NHL

Indication: Untreated B-NHL
Phase: II

Investigator and Study Center:

Principal Investigator
Ajay K Gopal, MD
Professor, UW
Member, FHCC
Fred Hutchinson Cancer Center
825 Eastlake Ave. E. LG-650
Seattle, WA 98109
Telephone: (206) 606-2037

Lead Sub-Investigator
Solomon A Graf, MD
Assistant Professor, UW
Fred Hutchinson Cancer Center
825 Eastlake Ave. E. G3-200
Seattle, WA 98109
Telephone: (206) 277-4757

This is an investigator-initiated study. The principal investigator Ajay Gopal, 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.

PROTOCOL SUMMARY

Study Title: A Window Study of Ixazomib in Untreated Indolent B-NHL

Phase: II

Number of Patients: 36

Study Objectives:

Primary

- To assess the efficacy of ixazomib as monotherapy in untreated indolent B-NHL based on overall response rate (ORR).

Secondary

- To evaluate the efficacy parameters of ixazomib in untreated B-NHL, including the duration of response, progression-free survival, time to next treatment, and complete response rate.
- To evaluate the efficacy of ixazomib combined with rituximab in subjects with B-NHL.
- To evaluate the safety and tolerability of ixazomib in subjects with B-NHL.

Tertiary/Exploratory *(if applicable)*

- To evaluate clinical and biological prognostic and predictive biomarkers relative to treatment outcomes.

Overview of Study Design:

Eligible patients will be entered onto the study and receive oral ixazomib weekly. A window period of six 4-week cycles of ixazomib monotherapy will be give upfront. On completion of the window period, four weekly doses of intravenous rituximab infusions will be added as ixazomib is continued. Treatment with ixazomib will continue on 4-week cycles until unacceptable drug toxicity, disease progression, or other reason as described below.

The ORR of ixazomib monotherapy during the window period will be calculated before the addition of rituximab. The null hypothesis for ixazomib monotherapy in the upfront setting is an ORR < 40% and the alternative hypothesis is that the ORR exceeds 60%. A total of 36 patients will be treated.

Study Population:

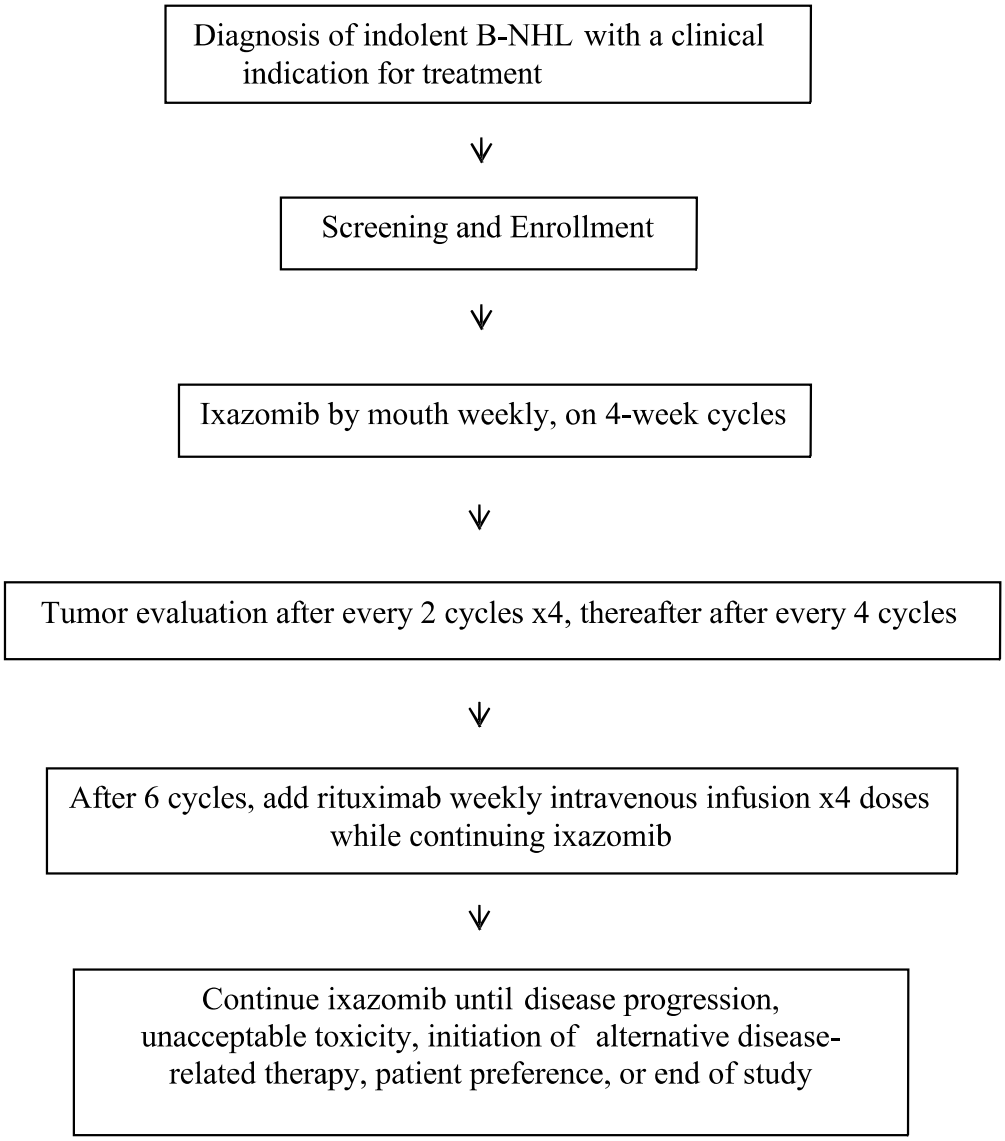
The study population will include patients with a diagnosis confirmed histopathologically or by flow cytometry of indolent B-NHL, including the subtypes CLL/SLL, FL, MCL, MZL, and WM/LPL. Patients will not have received standard systemic therapy for their B-NHL previously, except in cases of the MALT subtype of MZL treated with antibiotics.

At the time of enrollment, patients will have measurable disease and a clinical indication for treatment.

Duration of Study:

Anticipated enrollment period is 1-2 years, with total study time of approximately 5 years.

STUDY OVERVIEW DIAGRAM



SCHEDULE OF EVENTS

Study Calendar: One treatment cycle = 28 days

Required Procedures	Screening[6]	Treatment Phase	End of Treatment[12]
History and Physical			
Medical history	x		
Physical exam	x	X[9]	x
ECOG performance status	x	X[9]	x
Clinical disease assessment	x	X[9]	x
Adverse event assessment	x	X[9]	x
Labs and Imaging			
CBC and differential	X	X[10]	X
Comprehensive metabolic panel	X	X[10]	X
LDH	X	X[10]	X
Beta 2 Microglobulin	X		
SPEP and immunofixation[1]	X	X[11]	X
CT chest, abdomen, pelvis[2]	X	X[11]	X
FDG-PET (base of skull to proximal femur)[3]	X	X	
Bone marrow studies[4]	X	X	
Pregnancy test	X[7]		
Pathologic studies	X[8]	X[8]	
Tumor Assessment[5]	X	X[11]	X

[1] In cases of WM/LPL.

[2] In cases of radiographically measurable disease (see section 7.2). Note this may not be present for cases of CLL and WM. Imaging of the neck is suggested for clinically evident or previously described cervical disease.

[3] FDG-PET scans will be obtained in cases of suspected FDG-avid disease (see section 7.2). During treatment phase, FDG-PET should be performed to confirm metabolic CR in patients with stable PR on 2 consecutive CT staging exams or in patients with a CR based on CT staging and baseline FDG-avid disease to determine metabolic CR. A Deauville score should be assigned when restaging FDG-PET scan is performed

.

[4] If bone marrow involvement by B-NHL was previously shown then repeat bone marrow exam at screening is not required as it is assumed positive. Otherwise, bone marrow studies include aspirate and unilateral biopsy and should be performed at screening unless a waiver is approved by the study PI/ Sub-I. If all bone marrow studies are negative at screening, these do not need to be repeated. If bone marrow status is unknown or positive at screening, patients will need to a have bone marrow study for confirmation of a CR. A bone marrow study may be requested during the first 2 cycles of treatment for correlative molecular research purposes.

[5] Tumor assessment labs and/or imaging will be performed according to disease subtype (see section 7.2). Tumor assessment labs and/or imaging will also be performed as indicated per clinical standard of care (e.g. as appropriate for disease, to evaluate clinical suspicion of disease progression).

[6] Screening studies will be performed within 4 weeks of the first day of study drug administration with

the exception of radiographic imaging: CT scans may be performed within 6 weeks of the first day of study drug administration; FDG-PET scans may be performed within 8 weeks of the first day of the study drug administration. All screening studies must be performed after the completion of any radiation therapy or non-standard systemic therapy given for B-NHL or systemic antibiotics used to treat cases of MZL.

[7] Pregnancy test is only required in women of childbearing potential.

[8] Archival tumor samples are requested for pathologic confirmation and correlative biomarker analysis. If an archived specimen is not available or contains insufficient material, a fresh tumor biopsy (if clinically feasible) may be requested. A fresh tumor biopsy (if clinically feasible) may be requested during the first 2 cycles of treatment for correlative molecular research purposes. Correlative studies may be performed on any available tissue, including peripheral blood.

[9] Clinical assessment (physical exam including performance status, adverse event and clinical disease assessment) will be performed on Day 1 of each cycle (+/-3 days) through the first 8 cycles. After cycle 8, clinical assessments will be performed on Day 1 of each odd-numbered cycle (+/-6 days). For Cycle 1, Day 1, the screening clinical assessment may be used. A Cycle 1, Day 14 (+/-3 days) clinical assessment is strongly recommended.

[10] Labs will be performed on Day 1 (+/-3 days) of each cycle for the first 8 cycles. After cycle 8, labs will be performed on Day 1 (+/-6 days) of each cycle. Labs may be performed at local laboratories with appropriate review by the PI/ Sub-I. For Cycle 1, Day 1, labs performed within 14 days are acceptable. Cycle 1, Day 14 (+/-3 days) labs are strongly recommended.

[11] Treatment phase tumor evaluation labs and/or imaging will be performed every 8 weeks of therapy (+/- 6 days) during the first 32 weeks, and approximately every 16 weeks of therapy thereafter, or as indicated per clinical standard of care (e.g. as appropriate for disease, to evaluate clinical suspicion of disease progression).

[12] End-of-treatment evaluations should be done within 30 days of the last dose of ixazomib or prior to the start of a new anti-neoplastic drug, whichever is first. Tumor assessment labs and/or imaging will be performed at end-of-treatment evaluation only for subjects who did not have tumor assessment labs and/or imaging performed within 60 days of end-of-treatment.

Long-term follow-up should be done according to the patient's physicians standard of care. This may be performed at the patient's local physician's offices. Long-term follow-up will assess survival and disease progression; for clarification, subjects may be contacted by the study team until death, withdrawal of consent, lost to follow-up, or study termination by the sponsor-investigator, whichever occurs first.

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-HT_3	5-hydroxytryptamine 3 serotonin receptor
AE	adverse event
ALL	acute lymphoblastic leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myelogenous leukemia
ANC	absolute neutrophil count
API	active pharmaceutical ingredient
aPTT	activated partial thromboplastin time
Ara-C	Cytarabine
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
$AUC_{24\ hr}$	area under the plasma concentration versus time curve from zero to 24 hours
AUC_{inf}	area under the plasma concentration versus time curve from zero to infinity
AUC_{τ}	area under the plasma concentration versus time curve from zero to next dose
BCRP	breast cancer resistance protein
□hCG	beta-human chorionic gonadotropin
BID	bis in die; twice a day
BM	bone marrow
BSA	body surface area
BUN	blood urea nitrogen
BZD	Benzodiazepines
CBC	complete blood count
CFR	Code of Federal Regulations
CL	clearance, IV dosing
CL_P	plasma clearance
CL_{Total}	total clearance
C_{max}	single-dose maximum (peak) concentration
CNS	central nervous system

Abbreviation	Term
CO_2	carbon dioxide
CR	complete response
CRM	continual reassessment method
CRP	C-reactive protein
CSF-1R	colony-stimulating factor 1 receptor
CT	computed tomography
C_{trough}	single-dose end of dosing interval (trough) concentration
CV	coefficient of variation
CYP	cytochrome P_{450}
DLT	dose-limiting toxicity
DME	drug metabolizing enzymes
DNA	deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
EOS	End of Study (visit)
EOT	End of Treatment (visit)
EU	European Union
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GGT	gamma glutamyl transferase
GI	Gastrointestinal
GLP	Good Laboratory Practices
GM-CSF	granulocyte macrophage-colony stimulating factor
GMP	Good Manufacturing Practice
Hb	Hemoglobin
Hct	Hematocrit
HDPE	high-density polyethylene
hERG	human ether-à-go-go related gene
HIV	human immunodeficiency virus
HNSTD	highest nonseverely toxic dose

Abbreviation	Term
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous; intravenously
IVRS	interactive voice response system
K_i	inhibition constant
KPS	Karnofsky Performance Status
LDH	lactate dehydrogenase
LFT	liver function test(s)
MedDRA	Medical Dictionary for Regulatory Activities
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MRI	magnetic resonance imaging
MRU	medical resource utilization
MTD	maximum tolerated dose
MUGA	multiple gated acquisition (scan)
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NPO	nothing by mouth
NYHA	New York Heart Association
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease (disease progression)
Pgp	P-glycoprotein
PK	pharmacokinetic(s)
PO	*per os*; by mouth (orally)
PR	partial response
PRO	patient-reported outcome
PSA	prostate-specific antigen
QD	*quaque die*; each day; once daily

Abbreviation	Term
QID	*quater in die;* 4 times a day
QOD	*quaque altera die*; every other day
QOL	quality of life
QTc	rate-corrected QT interval (millisec) of electrocardiograph
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SC	Subcutaneous
SD	stable disease
SmPC	Summary of Product Characteristics
$t_{1/2}$	terminal disposition half-life
TGI	tumor growth inhibition
T_{max}	single-dose time to reach maximum (peak) concentration
UK	United Kingdom
ULN	upper limit of the normal range
US	United States
V_z	volume of distribution in the terminal phase
WBC	white blood cell
WHO	World Health Organization

1. BACKGROUND AND STUDY RATIONALE

1.1 Scientific Background

1.1.1 Disease Under Treatment

B-cell non-Hodgkin lymphoproliferative malignancies (B-NHL) encompass a variety of disease types that can be categorized according to how aggressively they behave. The relatively indolent B-NHL histologies include chronic lymphocytic leukemia / small lymphocytic lymphoma (CLL/SLL), follicular lymphoma (FL), marginal zone lymphoma (MZL), Waldenstrom macroglobulinemia / lymphoplasmacytic lymphoma (WM/LPL), and, in some circumstances, mantle cell lymphoma (MCL). These diseases tend to be slowly progressive and initially responsive to chemo- / immuno- therapies. Treatments are therefore recommended to improve overall survival, for palliation of symptoms, and with a goal of minimizing therapy-related toxicities.

The natural history of indolent B-NHL is of generally progressive disease that becomes increasingly less sensitive to available treatments: indolent B-NHL are considered incurable short of allogeneic stem cell transplantation. Therefore, novel therapies with good efficacy and low toxicity profiles are needed to improve the morbidity and mortality of these diseases.

1.1.2 Ixazomib

1.2 Preclinical Experience

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

1.3 Clinical Experience

Ixazomib is the first investigational oral proteasome inhibitor to enter clinical trials. Phase 1, phase 1/2, and phase 2 trials are ongoing in MM, systemic light-chain amyloidosis (AL amyloidosis), solid tumors, and lymphoma. In addition, phase 1 studies are ongoing in patients with renal impairment who have relapsed and/or refractory multiple myeloma (RRMM) or advanced solid tumors (Study C16015), in patients with hepatic impairment who have advanced solid tumors or hematologic malignancies (Study C16018), and in an absorption, distribution, metabolism, and excretion (ADME) study in patients with advanced solid tumors or lymphoma (Study C16016). Phase 3 trials in RRMM, newly diagnosed multiple myeloma (NDMM), and relapsed or refractory systemic light-chain amyloidosis (RRAL amyloidosis) are underway.

As of 27 March 2015, data are available from 901 patients who have received at least 1 dose of either the IV or oral ixazomib formulations across the clinical development program; in addition, 1513 patients have enrolled in 4 phase 3 clinical trials: 1) Placebo-controlled Study C16010 and Study C16010 China continuation study (CCS) of ixazomib versus placebo in combination with LenDex in patients with RRMM; 2) Placebo-controlled Study C16014 of ixazomib versus placebo in combination with LenDex in patients with NDMM; 3) Placebo-controlled Study

C16019 of ixazomib versus placebo in patients with NDMM; 4) Open-label Study C16011 of ixazomib and dexamethasone versus physician's choice of a dexamethasone-containing regimen in patients with AL amyloidosis. Ixazomib is available as an IV and oral formulation; however, only the oral formulation is currently being developed for commercialization. Regardless of the route of administration, in the twice-weekly dosing schedule ixazomib is given on Days 1, 4, 8, and 11 of a 21-day cycle, and in the weekly dosing schedule ixazomib is given on Days 1, 8, and 15 of a 28-day cycle. Schedules with longer cycles are being investigated in Study C16006.

1.4 Pharmacokinetics and Drug Metabolism

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

Metabolism appears to be the major route of elimination for ixazomib, with negligible urinary excretion of the parent drug (< 3% of dose). In vitro studies of liver microsomes show that ixazomib is metabolized by multiple cytochrome P450 enzymes (CYPs) and non-CYP enzymes/proteins. The rank order of relative biotransformation activity of the 5 major human CYP isozymes is 3A4 (34.2%) > 1A2 (30.7%) > 2D6 (14.7%) > 2C9 (12.1%) > 2C19 (< 1%). ixazomib is not an inhibitor of CYPs 1A2, 2C9, 2C19, 2D6, or 3A4, nor is it a time-dependent inhibitor of CYP3A4/5. The potential for ixazomib treatment to produce DDIs via CYP inhibition is inferred to be low; however, there may be a potential for DDIs with a concomitant strong CYP3A4 or CYP1A2 inhibitor because of the potential for first-pass metabolism when ixazomib is administered via the PO route and because of the moderate contribution of CYP3A4- and CYP1A2-mediated metabolism of ixazomib in human liver microsomes. ixazomib may be a weak substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance associated protein (MRP2) efflux pump transporters. ixazomib is not an inhibitor of P-gp, BCRP, and MRP2. The potential for DDIs with substrates or inhibitors of P-gp, BCRP, and MRP2 is, therefore, inferred to be low.

Clinical Study C16009 (Arm 1) with ketoconazole, a strong CYP3A4 inhibitor, showed a 2-fold increase in area under the plasma concentration versus time curve (AUC) in the presence of ketoconazole. This resulted in the continued exclusion of strong CYP3A4 inhibitors in ongoing/planned clinical studies. Further details on these studies are provided in the IB.

1.5 Clinical Trial Experience Using the Oral Formulation of Ixazomib

As of 27 March 2015, a total of 755 patients with differing malignancies (MM, AL amyloidosis, lymphoma, and nonhematologic cancers) have received at least 1 dose of ixazomib in phase 1, phase 1/2, and phase 2 studies evaluating the oral ixazomib formulation. These patients have been treated with different doses of ixazomib either as a single-agent treatment (163 patients), in combination with currently clinically available treatments (370 patients), or in clinical pharmacology/special population studies (208 patients). In addition, 1513 patients have enrolled in phase 3 Studies C16010, C16010CCS, C16014, C16019 (double-blind, placebo–controlled studies in MM), and Study C16011 (open–label study in AL amyloidosis).

Table 1-1 Clinical Studies of Oral Ixazomib

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

Table 1-1 Clinical Studies of Oral Ixazomib

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

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

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

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

Overview of the Oral Formulation of Ixazomib

Adverse events (AEs) observed to date (as of 27 March 2015) are generally reversible, manageable with standard medical interventions, and are dose dependent. The type of AEs are generally consistent across the patient populations treated to date, though some AEs may be more common either due to the patient population or the regimen being studied (eg, thrombocytopenia is more common with weekly single-agent ixazomib in RRMM than in RRAL amyloidosis; in RRMM, thrombocytopenia is more common with weekly single agent ixazomib than when given in combination with LenDex; nausea is common across studies; diarrhea is more common with weekly ixazomib in combination with LenDex than with single-agent ixazomib). Such differences may illustrate effects of the disease or prior therapy on the body (eg, on the bone marrow) as well as the side effect profile of the agents in a combination regimen. The more commonly observed (≥30% incidence) treatment-emergent AEs (TEAEs) from pooled data across clinical studies with oral ixazomib include nausea (40%), diarrhea (39%), fatigue (37%), rash (all terms; 33%), and vomiting (30%). The frequency of rash is noted in an aggregate because it is characterized in different ways; however, it is less common when considering individual preferred terms. An overview of the most frequent (at least 10%) AEs occurring in the pooled safety population from single-agent oral ixazomib Studies (C16003, C16004, C16007, and C16009) is shown in Table 1-2.

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

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

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

Primary System Organ Class Preferred Term	Oral Single Agent Total n = 201 n (%)
Neuropathy peripheral	21 (10)
Metabolism and nutrition disorders	107 (53)
Decreased appetite	64 (32)
Dehydration	37 (18)
Blood and lymphatic system disorders	98 (49)
Thrombocytopenia	68 (34)
Anemia	42 (21)
Neutropenia	29 (14)
Lymphopenia	20 (10)
Skin and subcutaneous tissue disorders	90 (45)
Rash macular[a]	23 (11)
Musculoskeletal and connective tissue disorders	93 (46)
Back pain	24 (12)
Arthralgia	28 (14)
Respiratory, thoracic and mediastinal disorders	78 (39)
Cough	28 (14)
Dyspnea	30 (15)
Infections and infestations	89 (44)
Upper respiratory tract infection	31 (15)

Source: Ixazomib Investigator's Brochure Edition 7

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

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

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

Treatment emergent is defined as any AE that occurs after administration of the first dose of any study drug through 30 days after the last dose of any study drug, any event that is considered drug-related regardless of the start date of the event, or any event that is present at baseline but worsens in intensity or is subsequently considered by the investigator to be drug-related.

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

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

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

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

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

Primary System Organ Class Preferred Term	Total Oral Combo Agent (5/6/8/13) n = 173 n (%)
Pain in extremity	31 (18)
Arthralgia	22 (13)
Respiratory, thoracic and mediastinal disorders	80 (46)
Cough	36 (21)
Dyspnea	26 (15)
Infections and infestations	92 (53)
Upper respiratory tract infection	35 (20)
Psychiatric disorders	73 (42)
Insomnia	50 (29)

Source: Ixazomib Investigator's Brochure Edition 7

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

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

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

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

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

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

Of particular relevance to this study (C16011) is the clinical experience from Studies C16004 and C16007 in which single-agent ixazomib is administered weekly in patients with RRMM or RRAL, respectively.

1.6 Relapsed and/or Refractory Multiple Myeloma

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

Study C16003 is an open-label, dose escalation, phase 1 study of ixazomib dosing on

a twice-weekly schedule on Days 1, 4, 8, and 11 of a 21-day cycle in adult patients with RRMM [10]. Study C16004 is an open-label, dose escalation, phase 1 study of ixazomib dosing on a weekly schedule on Days 1, 8, and 15 of a 28-day cycle in adults patients with RRMM. Both studies have now completed enrollment. The DLTs in Study C16003 were rash macular and thrombocytopenia and the DLTs in C16004 were nausea, diarrhea, vomiting, and erythema multiforme.

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

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

1.7 Newly Diagnosed Multiple Myeloma (NDMM)

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

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

1.8 Clinical Trial Experience Using the Intravenous Formulation of Ixazomib

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

1.9 Study Rationale

At diagnosis, indolent B-NHL are often managed with low-intensity systemic therapy such as single agent rituximab until an indication for more aggressive, cytotoxic, therapy is present or anticipated. This period represents an opportunity for testing novel, low- toxicity therapies with several advantages over the more conventional setting of relapsed or refractory disease. The most significant of these

advantages is that tumors are unexposed to prior anti-neoplastic agents that can result in additional genetic mutation and enhanced drug resistance, potentially decreasing the efficacy signal for a novel pharmaceutical. For a given disease and drug (used as mono- therapy), the maximum, or "ceiling," activity is apparent in the treatment-naïve setting; identification of this ceiling of activity can accelerate a drug's development and focus research efforts on those diseases for which benefit of the drug is most promising. Likewise, this study design can also rapidly exclude insufficiently effective drugs allowing research efforts to be devoted to more promising strategies. The importance of this opportunity is highlighted by the current National Comprehensive Cancer Center guidelines for indolent B-NHLs suggesting *"Given incurability with conventional therapy, consider investigational therapy as first-line of treatment."*

Ixazomib is a novel second-generation, orally bioavailable proteasome inhibitor (PI) that has shown promising preclinical efficacy in B-NHL models and success in an early-phase clinical trial in heavily pretreated, relapsed/refractory B-NHL [5]; it is approved by the FDA for use in relapsed MM. The ubiquitin-proteasome system (UPS) participates in the regulation of cellular proliferation, apoptosis, and cycle progression. Proteasome inhibition represents a well-described mechanism for disrupting cellular protein homeostasis, and, consequently, the health of a cell. The pathogenesis of B-NHL involves pathways whose components are processed by the UPS, including cyclins, members of the Bcl-2 protein family, and transcription factors NF-KB and c-Myc [11]. Inhibition of proteasome activity with the first-generation PI bortezomib showed benefit as mono-therapy in several types of lymphomas, including MCL [12] and various B-NHL histologies in the relapsed or refractory setting [13, 14]. Ixazomib possesses improved tissue penetration and antitumor activity *in vitro* compared with bortezomib [15] and thus represents a promising, novel approach in treating B-NHL. Importantly, emerging safety profile indicates that oral ixazomib is generally well tolerated with predominant toxicities that are largely reversible, able to be monitored by routine clinical examinations and manageable by dose reductions, discontinuation, or standard supportive care, making it an ideal candidate for upfront window testing in B-NHL previously untreated with standard systemic therapy.

The rationale for this study is to evaluate the efficacy of ixazomib in untreated, indolent B-NHL and gain a preliminary assessment of the ceiling of activity of this agent as monotherapy in these diseases.

To minimize the risk to patients receiving potentially ineffective first-line therapy with an experimental agent, a standard course of rituximab at a dose of 375 mg/m^2 per week x4 will be added after completion of 6 cycles of ixazomib monotherapy.

Rituximab as a single agent has broad activity in B-cell malignancies and established efficacy as a single agent in the indolent B-NHL to be studied herein.

The fixed dose of 4 mg PO weekly was selected based on several dose-escalation phase I ixazomib monotherapy studies (e.g. C16004 and C16009) that identified the MTD at this dose or higher.

As has been demonstrated for single-agent bortezomib in B-NHL, correlative studies may be pursued to evaluate the predictive ability of disease-specific biomarkers. These include tumor expression by immunohistochemistry of NF-KB p65, p21, CD68, and PSMA5 in addition to single-nucleotide polymorphism genotyping of PSMB1 P11A [5, 16, 17]. Further, gene expression profiling using fresh or formalin-fixed, paraffin-embedded tumor specimens may be performed to characterize lesions particular to pathways such as cell-cycling, tumorigenesis, and proliferation that affect disease response to ixazomib. Clinical features and validated prognostic data including cytogenetics for CLL/SLL, the MIPI score (see 11.5) and Ki-67 scores for MCL, the FLIPI score (see 11.4) score for MZL and FL, and the IPSS score (see 11.6) for WM/LPL will be scored and analyzed for their impact on ixazomib efficacy.

1.10 Potential Risks and Benefits

Please refer to the current ixazomib IB and SMA.

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

This study will be conducted in compliance with the protocol, good clinical practice (GCP), applicable regulatory requirements, and International Conference on Harmonisation (ICH) guidelinesexpanded development of ixazomib for the treatment of patients with advanced malignancy.

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

2. STUDY OBJECTIVES

2.1 Primary Objectives

To assess the efficacy of ixazomib as monotherapy in untreated indolent B-NHL based on overall response rate.

2.2 Secondary Objectives

- To evaluate efficacy parameters including the duration of response (DOR), progression-free survival (PFS), time to next therapy (TNT), and complete response rate (CR) of ixazomib in untreated indolent B-NHL.

- To evaluate the safety and tolerability of ixazomib in subjects with B-NHL.

- To evaluate the safety and tolerability of ixazomib plus rituximab in subjects with B-NHL.

- To evaluate the efficacy parameters including ORR, DOR, TNT, PFS, and CR of the combination of rituximab with ixazomib.

2.3 Tertiary/Exploratory Objectives

To evaluate clinical and biological prognostic and predictive biomarkers relative to treatment outcomes of ixazomib in indolent B-NHL.

3. STUDY ENDPOINTS

3.1 Primary Endpoints

Overall response rate (CR + PR)

3.2 Secondary Endpoints

Efficacy

- Duration of response (DOR)
- Progression-free survival (PFS)
- Overall survival (OS)
- Complete response rate (CR)
- Time to next antineoplastic therapy (TNT)

Safety/Tolerability

- Frequency, severity, and relatedness of adverse events (AEs)
- Frequency of AEs requiring discontinuation of study drug or dose reductions

3.3 Tertiary/Exploratory Endpoints (data to be collected whenever possible)

- Identification of clinical features (i.e. MIPI score, FLIPI score, IPSS score) and biomarkers (i.e. cytogenetics, Ki-67) that predict response to ixazomib
- Perform SNP genotyping for PSMB1 P11A and correlate with response to ixazomib and ixazomib plus rituximab
- Perform gene expression profiling on tumor specimens and correlate with response to ixazomib
- Analyze by IHC tumor expression of CD68, NF-KB p65, p27, and PSMA5 and correlate with response to ixazomib and ixazomib plus rituximab

4. STUDY DESIGN

4.1 Overview of Study Design

Screening and Pretreatment Assessments

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before the first administration of ixazomib. Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations.

With the exception of radiographic imaging, screening and pretreatment tests and evaluations will be performed within 4 weeks of Cycle 1, Day 1 (defined as the day of first dose of study drug). Imaging performed as standard-of-care within 6 weeks of Cycle 1, Day 1 (or 8 weeks of Cycle 1, Day 1 in the case of FDG-PET imaging) may be used. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to study entry may be used; such tests do not need to be repeated for screening.

See the study calendar for the schedule of screening and pretreatment assessments.

Assessments during Treatment

See the study calendar for the schedule of treatment assessments.

Study Completion Assessment

Patients who discontinue treatment will be asked to return to the FHCC within 30 days after the last ixazomib administration for a follow-up visit. The visit at which response assessment shows progressive disease may be used as the early termination visit.

See the study calendar for the details of the assessment to be performed at completion / early termination.

Follow-up Assessments

Long-term follow-up should be done with and according to the patient's physician. This can be performed in conjunction with the patient's local MD; patients do not need to return to the FHCC. Long-term follow-up will assess survival and disease progression; subjects will be contacted until death, subject withdrawal of consent, lost to follow-up, or study termination by the sponsor-investigator, whichever occurs first.

4.2 Number of Patients

A total of 36 patients will be enrolled. Enrollment will be defined as the day the subject is registered and assigned a study-specific subject number. Estimated distribution of the study population by gender, race, and ethnicity:

Table 4-1 Estimated distribution of patients by ethnicity, race, and gender

Ethnic / Racial Category	Females	Males
American Indian/Alaska Native		
Asian	1	1
Native Hawaiian or Other Pacific Islander		
Black or African American		1
White	16	16
More than one race		
Unknown or not reported	1	
Total of all subjects	18	18

4.3 Duration of Treatment

Ixazomib may be continued until disease progression, unacceptable toxicity, initiation of alternative disease-related therapy, or patient preference. Disease progression prior to initiation of rituximab requires discontinuation of treatment. For subjects that receive rituximab, treatment may continue absent disease progression beyond pre-rituximab baseline.

4.4 Duration of Study

The study duration will encompass the screening period, treatment phase, and follow-up period. The screening period is a maximum of 28 days and the treatment phase will be variable based on response to therapy and tolerance of therapy. Accrual is anticipated to take 1-2 years. During the follow-up period, patients will be followed for long-term including survival and disease progression; maximum follow-up will be 3 years after completing therapy. All study participants will stop study treatment at 5 years or at 1 year following the version date of this protocol modification (15 November 2022), whichever occurs later.

5. STUDY POPULATION

5.1 Inclusion Criteria

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

- Male or female patients 18 years or older
- Voluntary written consent must be given before performance of any study related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

Female patients who:

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

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

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

Patients must have a diagnosis of one of the following B-NHL malignancies: CLL/SLL, FL, MCL, MZL, or WM/LPL. Patients with MALT subtype of MZL may have relapsed or refractory disease after a course of antibiotic therapy. Otherwise, patients will not have received standard systemic treatment for their B-NHL before the time of study enrollment. Standard systemic therapy is defined by including any of the following agents, representing a comprehensive list of recommended front-line agents used in the treatment of B-NHL: cytotoxic chemotherapies (bendamustine, cyclophosphamide, doxorubicin, vincristine, chlorambucil, cytarabine, gemcitabine, platinum drugs, etoposide); anti-CD20 antibodies (obinutuzumab, ofatumumab, rituximab); lenalidomide; ibritumomab tiuxetan; proteasome inhibitors (bortezomib, carfilzomib); tyrosine kinase inhibitors (ibrutinib, acalabrutinib, idelalisib); alemtuzumab; corticosteroids unless given for an indication other than treating the B-NHL; or other therapy as determined by the PI.

Table 5-1 Criteria for diagnosis according to disease type

Disease	Criteria for diagnosis
CLL/SLL	Histopathologic or flow cytometric confirmation
FL	Histopathologic confirmation
MZL	Histopathologic confirmation
MCL	Histopathologic confirmation
WM/LPL	Per WHO criteria, see Appendix 11.12

1. Eastern Cooperative Oncology Group (ECOG) performance status and/or other performance status 0, 1, or 2.
2. Patients must meet the following clinical laboratory criteria:
    - Absolute neutrophil count (ANC) ≥1,000/mm3 or ≥500/mm3 if neutropenia is attributed to B-NHL (involvement of bone marrow) without growth factor support and platelet count ≥100,000/mm3 or ≥75,000/mm3 if thrombocytopenia is attributed to B-NHL (involvement of bone marrow or due to splenomegaly or immune thrombocytopenic purpura). Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days before study enrollment.
    - Total bilirubin ≤1.5 x the upper limit of the normal range (ULN).
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 x ULN.
    - Calculated creatinine clearance ≥30 mL/min (see Section 11.2).
3. Patients are required to meet criteria for initiation of therapy for their B-NHL according to published guidelines by the National Comprehensive Cancer Network (NCCN) (see appendix 11.7).
4. Patients must have measurable disease defined by at least one of the following criteria:
    - Lesions greater than 1.5 cm that can be accurately measured in two dimensions by CT (preferred) or MRI, and are not included in any prior field of radiation given to treat B-NHL.
    - In patients with CLL, circulating lymphocytes ≥ 5,000 / mm^3.
    - In patients with WM/LPL, measurable serum monoclonal IgM.

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. Major surgery within 14 days before enrollment.
3. Known central nervous system involvement.
4. Infection requiring systemic antibiotic therapy or other serious infection within 14 days before study enrollment.
5. Evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, cardiac arrhythmias, or congestive heart failure, and unstable angina or myocardial infarction within the past 6 months.
6. Systemic treatment, within 14 days before the first dose of ixazomib, with strong inhibitors of CYP1A2 (fluvoxamine, enoxacin, ciprofloxacin), strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, posaconazole) or strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort.
7. Known ongoing or known active systemic infection, known active hepatitis B or C virus infection, or known human immunodeficiency virus (HIV) positive.
8. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
9. Known allergy to ixazomib, its analogues, or excipients in the various formulations of ixazomib.
10. Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of ixazomib including difficulty swallowing.
11. Diagnosed or treated for another malignancy within 2 years before study enrollment or previously diagnosed (>2 years before study enrollment) with another malignancy and have any evidence of residual disease that is symptomatic or requiring treatment. (This may be waived at the discretion of the Principal Investigator for patients in complete remission if they have not received systemic therapy). Patients with non-melanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.
12. Patient has ≥Grade 2 peripheral neuropathy, or Grade 1 with pain on clinical examination during the screening period.
13. Participation in other clinical trials with other investigational agents not included in this trial, within 21 days of the start of this trial and throughout the duration of this trial.
14. Patients may not have impending organ compromise from disease as assessed by their treating physician.
15. Prior treatment of B-NHL with radiation therapy, non-standard systemic therapy, or antibiotics (in cases of MZL) within 21 days of the first dose of ixazomib.

6. STUDY DRUG

6.1 Description of Investigational Agents

Ixazomib Capsules

The ixazomib drug product is provided in strengths of 4.0, 3.0, 2.3, 2.0, 0.5 and 0.2mg capsules as the active boronic acid. The different dose strengths are differentiated by both capsule size and color as described below:

Dose Strength	Capsule Size	Capsule Color
4.0 mg	Size 4	Ivory
3.0 mg	Size 3	Light gray
2.3 mg	Size 2	Light pink
2.0 mg	Size 2	Swedish orange
0.5 mg	Size 3	Dark green
0.2 mg	Size 4	White opaque

6.2 Study Drug Administration

Ixazomib Administration

All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified sub-investigator(s). Patients should be monitored for toxicity, as necessary, and doses of ixazomib should be modified as needed to accommodate patient tolerance to treatment; this may include symptomatic treatment, dose interruptions, and adjustments of ixazomib dose (see Section 6.2).

Capsules of ixazomib will also be referred to as study drug. Study drug will be supplied by Millennium as capsules of 0.2, 0.5, and 2.0 mg, or as capsules of 2.3, 3.0 and 4.0 mg ixazomib, depending on available ixazomib formulation.

The prescribed administration of ixazomib doses in this study is 4 mg ixazomib q7 days in a q28 day cycle. Sufficient drug will be dispensed for each interval of evaluation at the FHCC, that is, either for 1 or 2 cycles of therapy.

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

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

6.2.1 Study Drug Destruction

Ixazomib Destruction

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

6.3 Administration of Rituximab

Rituximab will be administered at a standard dose of 375 mg/m^2 by intravenous infusion weekly for 4 consecutive weeks upon completion of the 6-cycle window period of ixazomib monotherapy. Rituximab will be administered per institution standard treatment plan with medications for infusion-reaction prophylaxis and/or treatment given at the discretion of the investigator. Ixazomib will be continued uninterrupted during and after the rituximab therapy. Dose modification or delay to rituximab may be made according to the discretion of the investigator.

6.4 Dose-Modification Guidelines

Study drug dose modifications may change depending on the disease and combination with other drug(s).

If a new combination study, an attempt should be made to integrate dose modifications for the combination for each AE.

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 $\geq 500/mm^3$.
- Platelet count must be $\geq 50{,}000/mm^3$.
- Non-hematologic toxicities, attributable to ixazomib (except for alopecia) and which required a dose hold, should, at the physician's discretion, generally be recovered to $\leq$ Grade 1 or 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 and/or Sub-Investigator.

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

Table 6-1 Ixazomib Dose Adjustments

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

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

Table 6-2 Ixazomib Dose Adjustments for Hematologic Toxicities

Criteria	Action
Platelet count less than 30,000/mm^3	• Hold Ixazomib dose. • Once the platelet counts have met the prespecified values (see Section 6.4.1), ixazomib may be reinitiated at its most recent dose. • If platelet count falls to less than 30,000/mm^3, hold ixazomib until counts have met the prespecified values (see Section 6.4.1) and then resume ixazomib at the next lower dose.
Absolute neutrophil count less than 500/mm^3	• Hold Ixazomib dose. • Once the ANC counts have met the prespecified values (see Section 6.4.1), ixazomib may be reinitiated at its most recent dose. • If absolute neutrophil count falls to less than 500/mm^3 again, hold ixazomib until counts have met the prespecified values (see Section 6.4.1) and then resume ixazomib at the next lower dose.

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

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
Grade 1 peripheral neuropathy	• No action	Grade 1 signs and symptoms: asymptomatic; without pain or loss of function; clinical or diagnostic observations only [21]
Grade 1 peripheral neuropathy with pain or Grade 2 peripheral neuropathy	• Hold study drug until resolution to Grade ≤ 1without pain or baseline	Grade 2 signs and symptoms: Moderate symptoms; limiting instrumental activities of daily living (ADL) [21]
Grade 2 peripheral neuropathy with pain or Grade 3 peripheral neuropathy	• Hold study drug until resolution to Grade ≤ 1 without pain 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 [21]
Grade 4 peripheral neuropathy	• Discontinue study drug	
Grade 2 Rash	• Symptomatic recommendations as per section 6.8	The investigator and project clinician may discuss considerations for dose modifications and symptom management.
Grade 2 nonhematologic toxicity judged to be related to study drug	• Study drug may be held at investigator's discretion	Symptom management as clinically indicated.
Grade 3 nonhematologic toxicity judged to be related to study drug If not recovered to ≤ Grade 1 or baseline within 4 weeks	• Hold study drug until resolution to Grade ≤ 1 or baseline • Reduce study drug 1 to next lower dose upon return to ≤ Grade 1 or baseline	Symptomatic recommendations noted in Section 6.6
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 PI and/or Sub-Investigator determines the patient is obtaining a clinical benefit and a waiver is provided.

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

6.5 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:
Systemic treatment with any of the following metabolizing enzyme inhibitors is not permitted during this study. A DDI with a strong inhibitor would increase MLN2238 exposure.

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

The following procedures are prohibited during the study:

- Any antineoplastic treatment except for drugs in this treatment regimen.
- Radiation therapy (the requirement for local radiation therapy generally indicates disease progression).
- Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days before study drug dosing.
- Adjuvant hormone therapy for breast or prostate cancer.

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

The following medications and procedures are permitted during the study:

Diphenhydramine, corticosteroids, and acetaminophen may be used at the discretion of the investigator for prophylaxis of rituximab infusion reactions.

Antiemetics, including 5-HT3 serotonin receptor antagonists, may be used at the discretion of the investigator.

Loperamide or other antidiarrheal should be used for symptomatic diarrhea at discretion of the investigator. The dose and regimen will be according to institutional guidelines.

IVF should be given to prevent volume depletion.

Growth factors (eg, granulocyte colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF], recombinant erythropoietin) are permitted. Their use should follow published guidelines and/or institutional practice . Erythropoietin will be allowed in this study. Their use should follow published guidelines and/or institutional practice.

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

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.

6.7 Precautions and Restrictions

Fluid deficits should be corrected before and throughout treatment.
Nonsteroidal anti-inflammatory drugs (NSAIDs) induced prevalence of nephrotoxicity is relatively low; however, given the wide use of these agents many persons are at risk, including for example, patients with cardio-renal disease, dehydration, and the aging kidney. NSAIDs should be avoided with impaired renal function given reported NSAID-induced renal failure in patients with decreased renal function.

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

should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following criteria:

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

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

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

6.8 Management of Clinical Events *(if applicable)*

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

Prophylaxis Against Risk of Reactivation of Herpes Infection

Patients may be at an increased risk of infection including reactivation of herpes zoster and herpes simplex viruses. Prophylactic antiviral therapy with, for example, acyclovir or valacyclovir is recommended during the course of treatment with ixazomib. Other antivirals are also acceptable.

Nausea and/or Vomiting

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

Diarrhea

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 Table 6-2 when thrombocytopenia occurs. Therapy can be reinitiated at a reduced level upon recovery of platelet counts. A rare risk is thrombotic thrombocytopenic purpura (TTP), a rare blood disorder where blood clots form in small blood vessels throughout the body characterized by thrombocytopenia, petechiae, fever, or possibly more serious signs and symptoms. TTP should be managed symptomatically according to standard medical practice.

Neutropenia

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 when neutropenia occurs, as noted in the dose modification recommendations in Table 6-2.

Fluid Deficits

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 deficits should be corrected before initiation of study drug and during treatment and as needed during therapy.

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

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.

6.9 Preparation, Reconstitution, and Dispensing

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

6.10 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.

6.11 Storage, Handling, and Accountability

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

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

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

In case of contact with the powder (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.

6.12 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.

6.13 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 (see section 4.3)
- Study terminated
- Pregnancy (patient must be discontinued)
- Other

At the time of withdrawal, all study procedures outlined for the End of Study visit should be completed whenever possible. 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

This study is designed to assess the efficacy of ixazomib in patients with untreated indolent B-NHL.

7.1.1 Determination of Sample Size

The sample size was determined to gain a preliminary assessment of the efficacy of ixazomib in untreated subtypes of B-NHL. The ORR for effective single-agent therapy in patients with indolent B-NHL is approximately 40 to 70% [19]. In this single-stage phase II study, the null hypothesis that the true response rate is $\leq 40\%$ will be tested against the alternative hypothesis that the true response rate is $\geq 60\%$ with a type I error rate of 8% and a power of 85%. An ORR of at least 19 out of 36 will be required to conclude promising efficacy.

7.1.2 Randomization and Stratification

Subjects will not be randomized or stratified for study entry.

7.1.3 Populations for Analysis

Efficacy will be evaluated at pre-specified restaging evaluations. Subjects must complete the first scheduled tumor evaluation or have progressive disease or intolerance of ixazomib prior to the first scheduled tumor evaluation to be evaluable for efficacy.

Safety and tolerability will be evaluated in all subjects that received at least 1 dose of ixazomib.

7.1.4 Demographic and Baseline Characteristics

Subject demographics (including age, sex, and race/ethnicity) and other baseline characteristics (including ECOG performance status, presence of B symptoms) and prognostic variables according to disease histology (# of nodal sites, LDH, hemoglobin, and Ann Arbor disease stage for FL and MZL; LDH and WBC for MCL; CBC with differential and FISH and cytogenetics analysis for CLL/SLL; CBC, SPEP, and beta-2 microglobulin for WM/LPL) will be recorded and summarized. Summary statistics will include means, standard deviations, and medians for continuous variables and proportions for categorical variables.

7.2 Efficacy Analysis

7.2.1 Criteria for Assessment of Disease

Tumor imaging and assessment of disease will be performed according to each disease subtype.

7.2.2 Follicular lymphoma and Mantle Cell Lymphoma

FDG-PET imaging will be required during study screening. Contrast-enhanced computed tomography (CT) of the chest, abdomen, and pelvis will be performed at each tumor assessment. FDG-PET should be performed to confirm metabolic CR in patients with stable PR on 2 consecutive CT staging exams or in patients with a CR

based on CT staging and baseline FDG-avid disease to determine metabolic CR. For measurement of response, 2014 criteria as described in "Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification" will be used (see Appendix 11.10) [20]. A Deauville score should be assigned when restaging PET is performed. CT imaging of the neck will be performed as indicated for standard of care.

All CT scans should be performed with IV contrast unless contraindicated, and abdominal and pelvis scans should be performed with oral contrast.

7.2.3 Marginal Zone Lymphoma and Cases of Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma and Waldenstrom Macroglobulinemia / Lymphoplasmacytic Lymphoma in which Nodal Disease is Known or Suspected

CT of the chest, abdomen, and pelvis will be performed at each tumor assessment. For measurement of response, 2014 criteria as described in "Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification" will be used (see Appendix 11.10) [20]. CT imaging of the neck will be performed as indicated for standard of care.

All CT scans should be performed with IV contrast unless contraindicated, and abdominal and pelvis scans should be performed with oral contrast.

7.2.4 Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma

CBC and differential will be performed on peripheral blood samples at each tumor assessment. For measurement of response, 2008 criteria as described in "Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines" will be used (see Appendix 11.11) [21].

7.2.5 Waldenstrom Macroglobulinemia / Lymphoplasmacytic Lymphoma

Serum protein electrophoresis (SPEP) and immunofixation will be performed on peripheral blood samples at each tumor assessment. For measurement of response, 2011 criteria as described in "Report from the Sixth International Workshop on Waldenström's Macroglobulinemia" will be used (see Appendix 11.12) [22].

7.2.6 Bone marrow aspirate and biopsy

A bone marrow aspirate and biopsy will be obtained before the first dose of study drug, and for confirmation of CR when indicated. Bone marrow aspirate and biopsy requirements may be waived by the Sponsor-Investigator or sub-Investigator. These samples will be evaluated locally.

7.3 Primary Efficacy Endpoint

Response assessments will be performed by the investigators. All measurable disease should be documented at screening and re-assessed at each subsequent tumor evaluation.

All patients treated with ixazomib will be considered evaluable for assessment of

response, with the following exceptions: 1) patients who missed ≥ 50% of scheduled doses of ixazomib prior to first scheduled treatment-phase tumor evaluation, unless due to related AE or progressive disease, will not be considered evaluable for assessment of response; 2) patients who did not undergo scheduled treatment-phase tumor evaluation, unless due to progressive disease, will not be considered evaluable for assessment of response.

The primary efficacy endpoint is the overall response rate (CR + PR for CLL/SLL, FL, MZL, and MCL; CR + Very Good PR + PR + Minor Response for WM/LPL) as assessed by the investigators. ORR will be calculated for all treated patients for each disease cohort. The corresponding 95% two-sided confidence interval will be derived.

7.4 Secondary Efficacy Endpoints

7.4.1 Duration of Response

In each disease cohort, for subjects achieving objective response as assessed by investigators, their duration of response as assessed by investigators will be calculated to determine durability. Duration of response will be measured from the time by which the measurement criteria are met for CR or PR, whichever is recorded first, until death or the first date by which recurrent or progressive disease is objectively documented. Subjects who are progression-free and alive at the time of clinical cut-off, or have unknown status will be censored at the last tumor assessment.

Non-responders will be excluded from the analysis of DOR. Kaplan Meier methodology will be used to estimate event-free curves.

7.4.2 Progression Free Survival

PFS will be measured for each disease cohort as time from the first study drug administration to the first occurrence of lymphoma progression or death from any cause.

Data for subjects without disease progression or death will be censored at the date of the last tumor assessment. Kaplan-Meier methodology will be used to estimate the event-free curves.

7.4.3 Time to Additional Anti-neoplastic Treatment

For each disease cohort the time to additional anti-neoplastic treatment will be measured from the time of first study drug administration until the date of subsequent the first subsequent therapy given to treat the B-NHL. Data for subjects that have not received additional anti-neoplastic therapy will be censored at the date of last known contact.

7.4.4 Pharmacokinetics/Pharmacodynamics/Biomarkers

Biomarker data may be collected on all subjects enrolled on study and examined for correlation of response to ixazomib in aggregate and with independent cohorts.

Samples of tumor tissue (fresh or formalin-fixed, paraffin-embedded) may be analyzed by immunohistochemistry to evaluate expression of proteins NF-KB p65,

p21, CD68, and PSMA5. Samples of peripheral blood and tumor tissue (fresh or formalin-fixed, paraffin-embedded) may additionally be studied using by SNP genotyping for PSMB1 P11A and with gene expression profiling to characterize candidate lesions particular to cell-cycling and proliferation pathways. Clinical features and validated prognostic data including cytogenetics for CLL/SLL, the MIPI score and Ki-67 scores for MCL, the FLIPI score for MZL and FL, and the IPSS score for WM/LPL will be scored and analyzed for their impact on response to ixazomib in independent cohorts only.

7.4.5 Safety Analysis

Adverse events and serious adverse events as defined in section 8 will be reviewed internally on an ongoing basis to identify safety concerns. Safety data will be evaluated in aggregate across the study cohorts. Analysis of safety data will be conducted on the safety population, which includes enrolled subjects who receive at least 1 dose of ixazomib. Safety summaries will include tabulations in the form of tables. The frequency of treatment-emergent AE's will be summarized. Additional AE summaries will include AE frequency by AE severity and relationship to the study drug.

AE's requiring discontinuation of the study drug will be summarized separately, both overall and by AE severity and by relationship to the study drug. Clinically significant abnormal laboratory values will be summarized over study visits.

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.

8.1.2 Serious Adverse Event Definition

Serious AE (SAE) means any untoward medical occurrence that at any dose:

1. Results in **death.**
2. Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
3. Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph below on planned hospitalizations).
4. Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
5. Is a **congenital anomaly/birth defect**.
6. Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with

events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

8.2 Procedures for Reporting Serious Adverse Events

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

Adverse Events which are **serious** must be reported to Millennium Pharmacovigilance (or designee) from the date the participant signs Informed Consent through 30 days after administration of the last 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).

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

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

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

- **Fatal and Life Threatening SAEs** within 24 hours if possible but no later than 4 calendar days 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 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 NCCN version specified in the protocol, as a guideline, whenever possible (see Appendix 11.7)
- **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 4.0.

In the event that this is a multisite study, the sponsor-investigator is responsible to ensure that the SAE reports are sent to Millennium Pharmacovigilance (or designee) from all sites participating in the study. Sub-investigators must report all SAEs to the sponsor-investigator so that the sponsor-investigator can meet his/her foregoing reporting obligations to the required regulatory agencies and to Millennium Pharmacovigilance, unless otherwise agreed between the sponsor-investigator and sub-investigator(s).
Relationship to all study drugs for each SAE will be determined by the investigator or sub-investigator by responding yes or no to the question: Is there a reasonable possibility that the AE is associated with the study drug(s)?

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

SAE and Pregnancy Reporting Contact Information

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

Suggested Reporting Form:

- SAE Report Form (provided by Millennium)

- US FDA MedWatch 3500A
  https://www.fda.gov/downloads/aboutfda/reportsmanualsforms/forms/ucm048334.pdf
- 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, 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 and Safety Monitoring Plan

Institutional support of trial monitoring will be in accordance with the FHCRC/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, FHCRC Clinical Research Support coordinates data and compliance monitoring conducted by consultants, contract research organizations, or FHCRC employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP.

In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), FHCRC Scientific Review Committee (SRC) and the FHCRC/University of Washington Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating patients. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state and federal guidelines.

9.2 Product Complaints

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

For Product Complaints:
Call MedComm Solutions at: 1-877-674-3784 (1-877-MPI DRUG)
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. 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. . ASH Annual Meeting Abstracts 2010; 116(21): p. abstr 1813.
2. 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. 53rd ASH Annual Meeting and Exposition. San Diego, CA. 2011.
3. Chow LQ, et al. MLN9708, an investigational proteasome inhibitor, in patients with solid tumors; Updated phase 1 results Head and Neck Symposium. Phoenix, AZ 2012.
4. 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. . 17th EHA Annual Congress. Amsterdam, the Netherlands. 2012. .
5. Assouline SE, Chang J, Cheson BD et al. Phase 1 dose-escalation study of IV ixazomib, an investigational proteasome inhibitor, in patients with relapsed/refractory lymphoma. Blood Cancer J 2014; 4: e251.
6. Kumar SK, Bensinger WI, Zimmerman TM et al. Phase 1 study of weekly dosing with the investigational oral proteasome inhibitor ixazomib in relapsed/refractory multiple myeloma. Blood 2014; 124: 1047-1055.
7. Kumar SK, Berdeja JG, Niesvizky R et al. Safety and tolerability of ixazomib, an oral proteasome inhibitor, in combination with lenalidomide and dexamethasone in patients with previously untreated multiple myeloma: an open-label phase 1/2 study. Lancet Oncol 2014; 15: 1503-1512.
8. Richardson PG, Baz R, Wang M et al. Phase 1 study of twice-weekly ixazomib, an oral proteasome inhibitor, in relapsed/refractory multiple myeloma patients. Blood 2014; 124: 1038-1046.
9. 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. 54th ASH Annual Meeting and Exposition. Atlanta, Georgia. 2012.
10. Kumar S. ea. Weekly dosing of the investigational oral proteasome inhibitor MLN9708 in patients (pts) with relapsed/refractory multiple myeloma (MM): A phase I study. ASCO Annual Meeting. Chicago, Illinois. 2012.
11. Suh KS, Tanaka T, Sarojini S et al. The role of the ubiquitin proteasome system in lymphoma. Crit Rev Oncol Hematol 2013; 87: 306-322.
12. Kane RC, Dagher R, Farrell A et al. Bortezomib for the treatment of mantle cell lymphoma. Clin Cancer Res 2007; 13: 5291-5294.
13. Goy A, Younes A, McLaughlin P et al. Phase II study of proteasome inhibitor bortezomib in relapsed or refractory B-cell non-Hodgkin's lymphoma. J Clin Oncol 2005; 23: 667-675.
14. O'Connor OA, Wright J, Moskowitz C et al. Phase II clinical experience with the novel proteasome inhibitor bortezomib in patients with indolent non-Hodgkin's lymphoma and mantle cell lymphoma. J Clin Oncol 2005; 23: 676-684.
15. Lee EC, Fitzgerald M, Bannerman B et al. Antitumor activity of the investigational proteasome inhibitor MLN9708 in mouse models of B-cell and plasma cell malignancies. Clin Cancer Res 2011; 17: 7313-7323.

16. Coiffier B, Li W, Henitz ED et al. Prespecified candidate biomarkers identify follicular lymphoma patients who achieved longer progression-free survival with bortezomib-rituximab versus rituximab. Clin Cancer Res 2013; 19: 2551-2561.
17. Goy A, Bernstein SH, McDonald A et al. Potential biomarkers of bortezomib activity in mantle cell lymphoma from the phase 2 PINNACLE trial. Leuk Lymphoma 2010; 51: 1269-1277.
18. Ardeshna KM, Qian W, Smith P et al. Rituximab versus a watch-and-wait approach in patients with advanced-stage, asymptomatic, non-bulky follicular lymphoma: an open-label randomised phase 3 trial. Lancet Oncol 2014; 15: 424-435.
19. Jacobson CA, Freedman AS. Is observation dead in follicular lymphoma? Still appropriate. J Natl Compr Canc Netw 2015; 13: 367-370.
20. Cheson BD, Fisher RI, Barrington SF et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014; 32: 3059-3068.
21. Hallek M, Cheson BD, Catovsky D et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood 2008; 111: 5446-5456.
22. Treon SP, Merlini G, Morra E et al. Report from the Sixth International Workshop on Waldenstrom's Macroglobulinemia. Clin Lymphoma Myeloma Leuk 2011; 11: 68-73.
23. Swerdlow A. ea. (Ed). World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues. . IARC Press, Lyon. 2008.
24. Cheson BD, Byrd JC, Rai KR et al. Novel targeted agents and the need to refine clinical end points in chronic lymphocytic leukemia. J Clin Oncol 2012; 30: 2820-2822.

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 pre-disease 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

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:

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

11.3 Ann Arbor Staging System

Ann Arbor staging system for lymphomas:

Stage I indicates that the cancer is located in a single region, usually one lymph node and the surrounding area. Stage I often will not have outward symptoms.

Stage II indicates that the cancer is located in two separate regions, an affected lymph node or organ and a second affected area, and that both affected areas are confined to one side of the diaphragm - that is, both are above the diaphragm, or both are below the diaphragm.

Stage III indicates that the cancer has spread to both sides of the diaphragm, including one organ or area near the lymph nodes or the spleen.

Stage IV indicates diffuse or disseminated involvement of one or more extralymphatic organs, including any involvement of the liver, bone marrow, or nodular involvement of the lungs.

These letters can be appended to some stages:

A or B: the absence of constitutional (B-type) symptoms is denoted by adding an "A" to the stage; the presence is denoted by adding a "B" to the stage.

E: is used if the disease is "extranodal" (not in the lymph nodes) or has spread from lymph nodes to adjacent tissue.

X: is used if the largest deposit is >10 cm large ("bulky disease").

S: is used if the disease has spread to the spleen.

11.4 MIPI Scoring System

Patients diagnosed with MCL are assigned points according to the following system; the sum of the points constitutes the MIPI score:

1. 0 points: Age less than 50 years, ECOG performance status of 0-1, LDH less than 0.67 of the upper limit of normal, or WBC of less than 6,700 cells/ μL

2. 1 point: Age 50-59, LDH 0.67-0.99 of the upper limit of normal, or WBC 6,700 to 9,999 cells/ μL

3. 2 points: Age 60-69, ECOG performance status of 2-4, LDH 1-1.49 times the upper limit of normal, or WBC 10,000-14,000 cells/ μL

4. 3 points: Age 70 or greater, LDH 1.5 times the upper limit of normal or greater, and WBC of 15,000 cells/ μL or greater

11.5 IPSS Scoring System

One point for each of the following risk factors is assigned to patients diagnosed with WM/LPL:

1. Age >65 years
2. Hemoglobin ≤11.5 g/dL
3. Platelet count $\leq 100 \times 10^9$/L
4. B2-microglobulin >3 mg/L
5. Serum monoclonal protein concentration >70 g/L

11.6 WHO Criteria for diagnosis of WM/LPL [23]

11.6.1 LPL

1. Neoplasm of small B lymphocytes, plasmacytoid lymphocytes, and plasma cells
2. Usually involving bone marrow and sometimes lymph nodes and spleen
3. Does not fulfill criteria of any other small B-cell lymphoid neoplasm that may also have plasmacytic differentiation

11.6.2 WM

LPL with bone marrow involvement and IgM monoclonal gammopathy of any concentration

11.7 NCCN Guidelines Version 2.2015: Indications for treatment of indolent B-NHL

1. Symptoms due to any indolent B-NHL
2. Threatened end-organ function due to any indolent B-NHL
3. Progressive cytopenia secondary to any indolent B-NHL
4. Steady progression of FL, MCL, MZL
5. Cryoglobulinemia due to WM/LPL
6. Cold agglutinin disease due to WM/LPL

11.8 The Lugano Response Classification: For FL, MZL, and MCL [20]

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	**Complete metabolic response**	Complete radiologic response (all of the following)
	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
Lymph nodes and extralymphatic sites	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	Not applicable

Response and Site	PET-CT–Based Response	CT-Based Response
	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	
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
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If	Regrowth of previously resolved lesions

Response and Site	PET-CT–Based Response	CT-Based Response
	uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	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.

11.9 Response and Progression Criteria for CLL [21, 24].

Parameter	CR (all criteria must be met)[1]	PR (all criteria from Group A and one from Group B must be met)	PD (at least one criteria from Group A of one from Group B must be met)[2]	Stable disease (all criteria must be met)
Group A				
Lymphadenopathy[3]	None > 1.5 cm	Decrease ≥50%[4]	Increase ≥50%or any new LN > 1.5 cm[5]	Change of -49% to +49%

Blood lymphocytes	< 4,000/ µL	Decrease ≥ 50% from baseline	Increase ≥ 50% over baseline (≥5,000/µL)[6]	Change of -49% to +49%
Hepatomegaly	None	Decrease ≥50%[7]	Increase ≥50%[8]	Change of -49% to +49%
Splenomegaly	None	Decrease ≥50%	Increase ≥50%	Change of -49% to +49%
Marrow	Normocellular, < 30% lymphocytes, no B-lymphoid nodules[9]			
Group B				
Platelet count	> 100,000 / µL[10]	> 100,000/µL or increase ≥ 50% over baseline	Decrease of ≥ 50% from baseline secondary to CLL	Change of -49% to +49%
Hemoglobin	> 11 g/dL	> 11 g/dL or increase ≥ 50% over baseline	Decrease of > 2 g/dL from baseline secondary to CLL	Increase to < 11 g/dL or < 50% over baseline or decrease < 2 g/dL
Neutrophils	> 1,500 / µL	> 1,500 / µL or > 50% improvement over baseline	Decrease of > 50% from baseline secondary to CLL	
Other considerations				
New lesions	None	None	Appearance of new palpable LN (> 1.5 cm in longest diameter) or any new extranodal lesion (regardless of size)	None
Non-Target Lesions	Nodes must be normal size as visually estimated; extranodal and other assessable disease should be absent	No change / decreased	Unequivocal progression	No change or decrease or non-substantial increase

Target extranodal disease	Absence of any extranodal disease by physical exam and CT scan	≥ 50% decrease in SPD	≥ 50% increase in the longest diameter of any extranodal lesion	Nor CR, CRi, PR, or SD

Transformation to a more aggressive histology (e.g. Richter syndrome) would also qualify as PD.
[1] CR also requires the lack of disease-related constitutional symptoms
[2] Transformation to a more aggressive histology (e.g. Richter syndrome) would also qualify as a PD
[3] Sum of the products of multiple LNs (as evaluated by CT scans in clinical trials). Note in eCRF if by physical examination only
[4] Sum products of up to 6 LNs or LN masses (target lesions), with no increase in an LN or new enlarged LN. Increase of <25% in small LNs (< 2cm) not significant. Decreases should be measured compared to baseline (pre-treatment) values.
[5] Increase in SPD of multiple nodes, or in greatest diameter of any previous site, or appearance of any new lymphadenopathy or organomegaly. Degree of change in LN or lymphocyte counts should be measured from nadir (lowest post-treatment) values.
[6] In the absence of other objective evidence of PD, lymphocytosis alone should not be considered an indicator of PD. Patients with lymphocytosis and no other evidence of PD should continue therapy until they develop at least one other criteria suggesting progressive disease other than lymphocytosis.
[7] If abnormal before therapy
[8] An increase in the previously noted enlargement of the liver or spleen by 50% or more or the de novo appearance of hepatomegaly or splenomegaly.
[9] Hypocellular marrow defines CRi (complete response with incomplete marrow recovery).
[10] Without the need for exogenous growth factors or transfusions.

11.10 RESPONSE CRITERIA FORWM/LPL [22]

Complete Response
IgM in normal range, and disappearance of monoclonal protein by immunofixation; no histologic evidence of bone marrow involvement, and resolution of any adenopathy/organomegaly (if present at baseline), along with no signs or symptoms attributable to WM. Reconfirmation of the CR status is required by repeat immunofixation studies.

Very Good Partial Response
A ≥90% reduction of the serum IgM and decrease in adenopathy/organomegaly (if present at baseline) on physical examination or on CT scan. No new symptoms or signs of active disease.

Partial Response
A ≥50% reduction of serum IgM and decrease in adenopathy/organomegaly (if present at baseline) on physical examination or on CT scan. No new symptoms or signs of active disease.

Minor Response
A ≥25% but <50% reduction of serum IgM. No new symptoms or signs of active disease.

Stable Disease
A <25% reduction and < 25% increase of serum IgM without progression of adenopathy/organomegaly, cytopenias, or clinically significant symptoms due to disease and/or signs of WM.

Progressive Disease
A ≥25% increase in serum IgM by protein confirmed by a second measurement or progression of clinically significant findings due to disease (i.e. anemia, thrombocytopenia, leukopenia, bulky adenopathy/organomegaly) or symptoms (unexplained recurrent fever >38.3C, drenching night sweats, ≥10% body weight loss, or hyperviscosity, neuropathy, symptomatic cryoglobulinemia, or amyloidosis) attributable to WM.

11.11 Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

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