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Phase II Study of Ibrutinib in Combination With Ixazomib in Patients With Waldenstrom Macroglobulinemia

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Mayo Clinic Cancer Center

Phase II study of Ibrutinib in combination with Ixazomib in patients with Waldenström Macroglobulinemia

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*No waivers of eligibility allowed

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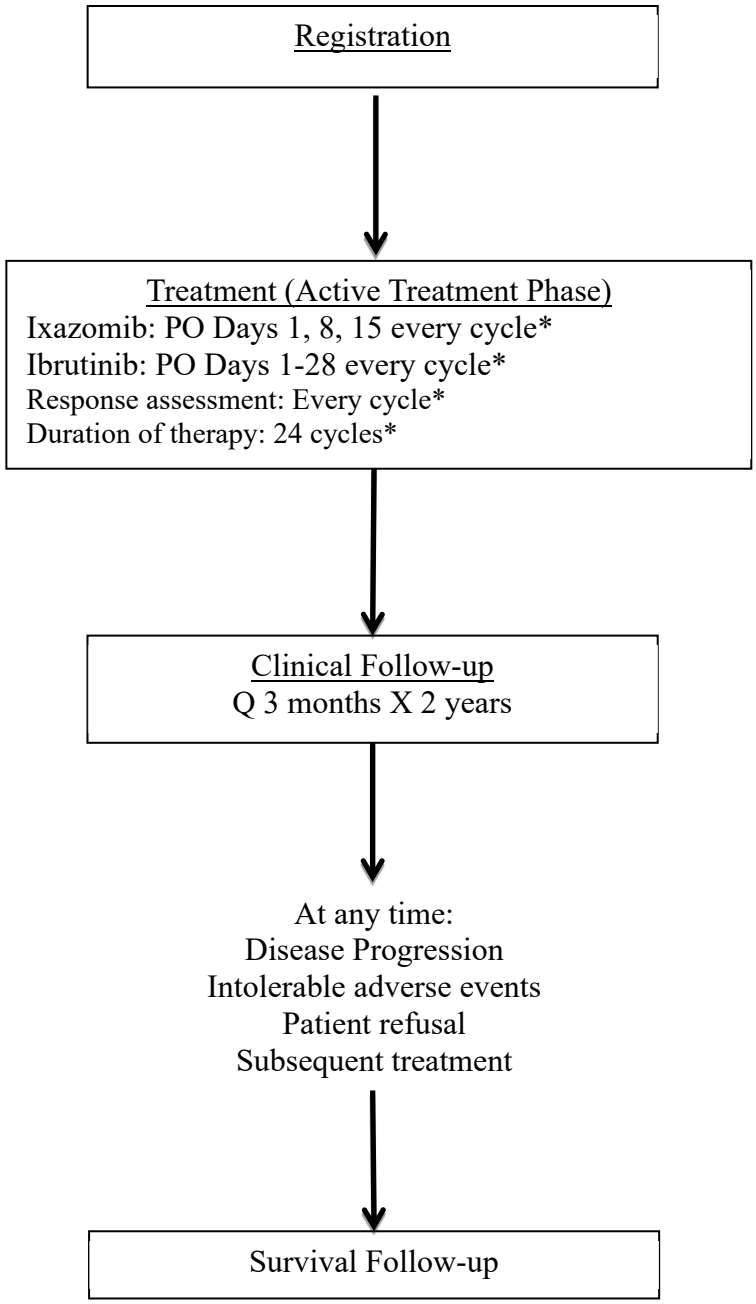
Schema



*Every cycle = 28 days (4 weeks - except at treatment completion where cycle length will be the number of treatment days in that cycle + 28 days)

Generic name: Ixazomib **Brand name(s): Ninlaro®** **Mayo Abbreviation:MLN9708** **Availability: Mayo Clinic Pharmacy**	**Generic name: Ibrutinib** **Brand name(s):Imbruvica®** **Mayo Abbreviation: PCI-32765** **Availability: Commercial**

1.0 Background

1.1 Waldenström macroglobulinemia

Waldenström macroglobulinemia (WM) is an incurable indolent B-cell neoplasm manifested by the accumulation of clonal immunoglobulin (Ig)M-secreting lymphoplasmacytic cells (Treon, Xu et al. 2015). WM is a rare disorder, with an incidence rate of about 3 cases per million people per year in the United States (ACS website).

Clinical Presentation: patients may have variable clinical presentation and the symptoms can be divided into three major clinical groups: (a) symptoms related to the underlying lymphoproliferative process (e.g., constitutional symptoms, cytopenias, or tissue infiltration), (b) hyperviscosity related to the overproduction of IgM, and (c) paraneoplastic neuropathy.

Patients with disease-related hemoglobin <10 g/L, platelets $<100 \times 10^9$/L, bulky adenopathy and/or organomegaly, symptomatic hyperviscosity, peripheral neuropathy, amyloidosis, cryoglobulinemia, cold-agglutinin disease, or transformed disease are often considered for therapy while asymptomatic patients can be monitored.

1.11 Disease biology

Understanding the biology of WM has revealed two critical survival pathways that exposed the vulnerability of the malignant cells.

The proteasome system:

WM cell survival is critically anchored to the viability of proteasomes, which form the principle component of the ubiquitin proteasome degradation system (UPS). The UPS regulates stability of numerous proteins such as p53, cyclin- dependent kinase inhibitors and nuclear transcription factor kappa-B (NFkB), all whose balance is crucial to the maintenance of normal cellular homeostasis. (LQ. 2012) Moreover, in WM cells that have a high protein turnover, UPS machinery is upregulated to prevent accumulation of misfolded proteins. (Assouline 2012). Proteasomes are comprised of a 26S barrel shaped structure that is flanked on both sides with two regulatory 19S caps. The ß rings of the 26S core form the catalytic components. Disruption of the catalytic core by proteasome inhibitors (PI) such as bortezomib, carfilzomib and ixazomib inhibits chymotrypsin-like activity at the ß5 subunits and this results in loss of WM cell viability. Importantly, the pleiotropic effects of the pro survival complex NFkB, which is expressed at high levels in WM cells (Lonial 2012), is attenuated by PI through the stabilization of its inhibitor (IkB) (Kumar 2011). It is therefore not surprising that inhibition of the UPS with PIs such as the first in class agent bortezomib has resulted in significant clinical benefit in over 80% of WM patients treated. Ixazomib is a newer, more tolerable and more patient convenient PI that effectively targets the proteasome and has demonstrated impressive anti-multiple myeloma (MM) activity in plasma cell cancers. Our preclinical evaluations have demonstrated its activity in models of WM.

BCR signaling:
More recently, it has been demonstrated that the pathological behavior of WM cells is a consequence of aberrant B-cell receptor (BCR) signaling due to activating mutations of the myeloid differentiation primary response gene 88 (MYD88L265P) and hyper-activation of Brutons tyrosine kinase (BTK) (Treon, Cao et al. 2014, Treon, Xu et al. 2015). Although individually distinct and qualified to drive WM pathogenesis, these molecular abnormalities often converge on the common effector element of NFkB. Together, the MYD88L265P/ IRAK1/4/ BTK complexes induce a signaling cascade that activates NFkB and the Signal Transducers and Activators of Transcription (STAT) family of factors (Kumar 2012). NFkB and STATs in turn regulate the expression and stability of several tumor promoting genes (c-MYC, IL-6, Bcl-xL, Gadd45b, IAPs) (Kumar 2011). Ibrutinib is an irreversible small molecule inhibitor of BTK that blocks signal transduction activity of the B-cell receptor (BCR) by disengaging BTKs interactions with PLC and MYD88 (Richardson 2012). Thus, downstream activation of NFkB and STAT signaling is mitigated resulting in decreased pro survival signals, direct induction of apoptosis and inhibition of cell homing towards chemokine's that facilitate adhesion (Richardson 2011., San Miguel 2012). Several lines of preclinical evidence in various B-cell lymphoma cell lines and now also in WM models attests to the tumoricidal effects of ibrutinib.

1.2 Treatment for WM

Up until 2015 there was no standard FDA therapy for the treatment of symptomatic WM. The therapeutic strategies for treatment of WM were primarily derived from experience in other plasma cell / B cell cancers with the use of steroids, chemotherapeutics (cyclophosphamide, doxorubicin), biologics (rituximab) and novel agents (such as the proteasome inhibitor bortezomib). Among these the highest single agent response rate was reached with bortezomib.

In January of 2015, ibrutinib was the first drug to receive FDA approval for treatment of WM. This approval was based on the demonstration of durable responses in a single arm, multi-center phase II clinical trial enrolling 63 patients with previously treated WM. The overall response rate (inclusive of complete response (CR), very good partial response (VGPR), and partial response (PR)) was 61.9% (95%CI 48.8, 73.9). Among these the responses consisted of VGPR (11.1%) and PR (50.8%) with none of the patients achieving a CR. The median duration of response has not been reached at the time of drug approval (range of 2.8+ to 18.8+ months) with a median time to response of 1.2 months.

1.3 Rationale

Waldenström macroglobulinemia (WM) is a rare and incurable indolent B-cell neoplasm manifested by the accumulation of clonal immunoglobulin (Ig) M-secreting lymphoplasmacytic cells. Since 2015, the Bruton tyrosine kinase (BTK) inhibitor ibrutinib has been approved for the treatment of WM. Over 80% of patients with Waldenström Macroglobulinemia (WM) demonstrate clinical benefit from treatment with ibrutinib. However, most of the clinical responses are limited to partial remission, which is consistent with ibrutinib's clinical activity in other B-cell cancers as well. Therefore,

opportunities remain to enhance the response rates through combination therapies. The proteasome inhibitor ixazomib (MLN-9708) is an attractive combination partner because it complements the biological activity of ibrutinib, may synergistically enhance its anti-WM effects and does not have an overlapping toxicity profile.

1.4 Study Design

This is a Phase II, single arm, open-label study to assess the efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics of the combination of ibrutinib and ixazomib administered to patients with WM. The study consists of a treatment phase, followed by an event-monitoring follow-up phase:

In the treatment phase, patients will receive ixazomib 4 mg PO on days 1, 8 and 15 and ibrutinib 420 mg PO daily in 4-weekly cycles. The response to therapy will be assessed every cycle, with imaging done every 2 cycles as necessary. Patients will receive additional cycles of treatment up to a maximum of 24 cycles or until progressive disease (PD), subsequent treatment, intolerable adverse effects, patient refusal, withdrawal of consent, or death.

After the patient has completed the treatment phase an end-of-treatment (EOT) visit will be scheduled 4 weeks after the last intake of study medication. After the EOT visit, the patients will go to clinical follow-up, followed by the survival follow-up phase in which patients will be followed up for survival status and start of new lines of therapy.

1.5 Correlative Research

1.51 *To determine the role of members of the BTK signalosome in achievement or lack thereof of response to Ibrutinib and Ixazomib:* The variability in extent of response to a therapeutic agent may suggest underlying adaptability of the WM clone through components of the BTK signalosome. Patients with B-cell malignancies treated with ibrutinib demonstrate upregulation of p-Akt and p-Erk (downstream mediators of BTK) in some (but not all) cases, suggesting that these pathways may contribute to survival of the malignant clone. It was also concluded in this work that these cells might not be dependent upon the proximal BTK pathways mediated apoptosis and thus, resistant to killing by Ibrutinib. To address this question we will establish the profile of BTK signalosome for each patient through determination of the mRNA (RT-PCR/nanostring assay; whole exome sequencing (WES), transcriptome analysis) and protein expression (western blot analysis) of members of the BTK signaling pathway and look for associations between this and eventual response (or lack thereof) to the treatment. The said tests will be done analyzing the lymphoplasmacytic cells enriched from the bone marrow samples collected at baseline, and then at the time of disease progression. This will help explore mechanisms of acquired resistance to ibrutinib when used with ixazomib. We will also look for pAKT, pS6 and pERK as indirect pharmacodynamic biomarkers analyzed in patient's PBMC collected as a peripheral blood sample.

1.52 *To explore biologic effects of ibrutinib and ixazomib on microenvironment in WM and correlate with response to treatment:* In cancer redirection of host immunity from a predominant Th2 to Th1 response can deliver antitumor response. Ibrutinib can

bind to ITK, a member of the TEC-kinase family, which mediates TCR signaling through PLCg, NFAT, NF-kappaB and MAPK. This results in activation and proliferation of CD8+ cells. Our hypothesis is that ibrutinib with ixazomib alters the Th2:Th1 balance in the blood and bone marrow microenvironment, skewing towards a more Th1 profile and this may translate into clinical efficacy. We further hypothesize that the robustness of the Th1 response will direct this combination's depth of response. We will assess this in bone marrow samples comparing the baseline sample to one collected after 1 cycle of treatment with ibrutinib and ixazomib using the MultiOmyx Tumor Infiltrating Lymphocytes panel for T helper (CD4+), Treg (FOXP3+), T cytotoxic (CD8+), B cells (CD20+), macrophage (CD68+), NK cells (CD56+), immunosuppression (PD-L1), CD138+, CD38+, ITK and BTK. Furthermore, BTK/ITK occupancy by Ibrutinib has been associated with response rates in other B-cell malignancies where this is an effective agent (CLL) but this has never been tested in WM. This assay will be performed to assess target coverage in bone marrow samples obtained from patients at the end of 1 cycle of treatment with ibrutinib and ixazomib. In addition, PBMC samples (2 ml of whole blood with heparin) from baseline and after 1 cycle of treatment will be assessed for:
Th1 cells (live+, CD19-, CD3+, CD4+, CD8-, IFNg+)
Th2 cells (live+, CD19-, CD3+, CD4+, CD8-, IL4+)
Th17 cells (live+, CD19-, CD3+, CD4+, CD8-, IL17+)
Treg cells (live+, CD19-, CD14-, CD3+, CD4+, CD25+, CD127-, FOXP3, CCR4+)

2.0 Goals

2.1 Primary Goal

The primary objective of this study is to determine the efficacy (as assessed by complete response [CR] rate) of the combination of ixazomib and ibrutinib in WM patients.

2.2 Secondary Goals

2.21 To assess the overall response rate (ORR=PR or better) in WM patients treated with ixazomib and ibrutinib.

2.22 To assess the time to progression (TTP) in WM patients treated with ixazomib and ibrutinib.

2.23 To further characterize the safety and toxicity of the combination of ibrutinib and ixazomib.

2.24 To assess the overall survival (OS) in WM patients treated with ixazomib and ibrutinib.

2.3 Correlative Research

2.31 To determine the role of members of the BTK signalosome in achievement or lack thereof of response to ibrutinib and ixazomib.

2.32 To explore biologic effects of ibrutinib and ixazomib on microenvironment in WM and correlate with response to treatment.

3.0 Registration Patient Eligibility

3.1 Inclusion Criteria

3.11 Age ≥ 18 years

3.12 Histological confirmation of WM. Patients may have newly diagnosed, relapsed, or refractory disease. (Definition: **Newly diagnosed**; Patients previously untreated for WM, **Relapse**; patients who have received prior treatment for WM and now have disease recurrence. **Refractory**; patients who have received anti-WM therapy and are noted to have progressive disease while on therapy, or those patients who demonstrated disease progression within 6 months of the last anti-WM treatment). NOTE: Ibrutinib naïve patients are allowed. If previously treated with ibrutinib, subject must have reached a response of at least SD and cannot have progressed while on ibrutinib. If subject stopped taking ibrutinib for reasons other than progression, they cannot have progressed for at least 6 months post last dose of ibrutinib.

3.13 Presence of measurable disease as defined by: presence of IgM paraprotein, measurable lymphadenopathy on imaging studies and/or physical exam, and/or bone marrow infiltration >10%. (Kapoor, 2017)

3.14 ECOG Performance Status (PS) of 0, 1, or 2 (Appendix 1).

3.15 The following laboratory values obtained ≤14 days prior to registration:

- ANC ≥1000/mm^3
- Platelet count ≥75,000/mm^3 (**NOTE:** Platelet transfusions in order to help patients meet eligibility criteria are not allowed)
- Hemoglobin ≥9.0 g/dL
- Total bilirubin ≤1.5 x upper limit of normal (ULN) unless due to Gilbert's syndrome, in which case the direct bilirubin must be ≤1.5 X ULN.
- Aspartate transaminase (AST) and alanine aminotransferase (ALT) ≤3 x ULN
- Calculated creatinine clearance must be ≥30 ml/min using the Cockcroft-Gault formula below:

Cockcroft-Gault Equation:

Creatinine clearance for males = $\dfrac{(140 - \text{age [years]})(\text{weight in kg})}{(72)(\text{serum creatinine in mg/dL})}$

Creatinine clearance for females = $\dfrac{(140 - \text{age [years]})(\text{weight in kg})(0.85)}{(72)(\text{serum creatinine in mg/dL})}$

3.16 Negative pregnancy test done at screening and ≤3 days (72 hours) prior to registration, for women of childbearing potential

3.17 Provide written informed consent.

3.18 Willingness to provide mandatory blood specimens and bone marrow specimens for correlative research.

3.19 Willingness to return to enrolling institution for follow-up

3.2 Exclusion Criteria

3.21 Failure to have fully recovered (i.e., ≤Grade 1 toxicity) from the reversible effects of prior treatment for WM.

3.22 Major surgical procedure (including open biopsy, excluding central line IV and portacath placement) within ≤14 days prior to initiating study treatment, or anticipation of the need for major surgery during the course of the study treatment.

3.23 Radiotherapy ≤14 days prior to registration. If the involved field is small, 7 days will be considered a sufficient interval between treatment and administration of the Ixazomib.

3.24 Systemic treatment, ≤14 days before registration, with strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or St. John's wort.

3.25 Systemic anti-cancer therapy or participation in other clinical trials, including those with other investigational agents not included in this trial, ≤ 28 days of registration and throughout the duration of active treatment in this trial.

3.26 Patients that have previously been treated with ixazomib, or participated in a study with ixazomib whether treated with ixazomib or not. **Prior bortezomib treatment is allowed as per:** Patients with prior exposure to bortezomib will be allowed if they do not have disease refractory to bortezomib).

3.27 Central nervous system involvement (Bing-Neel syndrome).

3.28 Infection requiring systemic antibiotic therapy or other serious infection ≤7 days prior to registration.

3.29a Evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, serious cardiac arrhythmia requiring medication (other than adequately rate-controlled atrial fibrillation), symptomatic congestive heart failure, unstable angina, stroke/TIA within the past 6 months or myocardial infarction within the past 6 months.

3.29b Known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent.

3.29c Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of ixazomib or ibrutinib, including difficulty swallowing.

3.29d History of any other prior malignancy. (**NOTE:** Exception to this are adequately treated non-melanoma skin cancers, any *in situ* cancer, adequately treated stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for at least two years prior to study enrollment).

3.29e Patient has ≥ Grade 2 peripheral neuropathy or Grade 1 peripheral neuropathy with pain on clinical examination during the screening period.

329 f Any of the following because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown.

- Pregnant women
- Nursing women
- Men or women of child bearing potential (WCBP) who are unwilling to employ effective contraception. Effective contraception would be defined as utilizing 2 simultaneous methods of contraception from the time of signing consent through 90 days after the last dose of the study drugs unless they agree to participate in true abstinence when this is in line with the preferred and usual lifestyle of the

subject. [WCBP: A female who is sexually mature and who: (1) has not undergone a hysterectomy or bilateral oophorectomy; or (2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months)].

3.29g Evidence of any other serious medical condition (such as psychiatric illness, infectious diseases, physical or laboratory findings) that may interfere with the planned treatment, affect compliance or place the patient at high risk from treatment-related complications or potentially interfere with the completion of the treatment as per the protocol.

3.29h Ongoing, active hepatitis B or C virus infection, or known human immunodeficiency virus (HIV) positive.

32.9i Liver disease with Child-Pugh class B or C liver dysfunction.

3.29j Current treatment with a combination of ibrutinib and strong CYP3A inhibitors.

4.0 Test Schedule

4.1 Test schedule for Waldenström Macroglobulinemia

Tests and procedures	≤ 28 days prior to registration	≤ 14 days prior to registration	Cycle 1 Day 1	Cycle 1 Day 8	Cycle 1 Day 15	Cycle 1 Day 22	Cycles 2-24 (During course of treatment)[11] Day 1	(End of treatment) *4 weeks after last study drug intake*	Clinical Follow-up Q 3 months X 2 years
Window			±3 days				±7 days		±7 days
Informed Consent	X								
Complete medical history[1]		X	X						
Physical exam, vital signs Wt, PS		X	X				X	X	X
Pregnancy test[2]		X							
Hematology group CBC w/diff		X	X	X	X	X	X	X	X
Chemistry group Sodium Chloride Potassium Magnesium Phosphate Uric acid BUN Glucose ALT/AST Alkaline phosphatase Total protein Total Bilirubin Direct Bilirubin Albumin Serum creatinine Creatinine clearance calcium		X	X	X	X	X	X	X	X

Tests and procedures	≤ 28 days prior to registration	≤ 14 days prior to registration	Cycle 1 Day 1	Cycle 1 Day 8	Cycle 1 Day 15	Cycle 1 Day 22	Cycles 2-24 (During course of treatment)[12] Day 1	(End of treatment) 4 weeks after last study drug intake	Clinical Follow-up Q 3 months X 2 years
Bone marrow aspirate and biopsy[3]	X						X	X	X
Electrophoresis of serum and urine (SPEP/UPEP)		X[9]					X[9]	X[9]	X[9]
Affected immunoglobulins[4]		X					X	X	X
Immunofixation serum and urine (IF)		X					X	X	X
Immunoglobulin free light chains (FLC)		X					X	X	X
Serum beta-2-microglobulin, LDH, serum viscosity		X					X	X	X
Tumor measurement[5]		X					X	X	X
EKG or ECHO or MUGA[6]		X					X	X	X
Adverse event monitoring		X	X	X	X	X	X	X	X
Patient Medication Diary (Appendix II)[7]			X				X	X	
Research Bone Marrow Aspirate Sample[R] (see Section 14.0)		X[10]					X[11]	X[11]	
Mandatory Research blood specimens (see Section 14.0)[8,R]		X[10]					X	X	

Cycle = 28 days (except at treatment completion where cycle length will be the number of treatment days in that cycle + 28 days)

1. Does not need to be repeated on cycle 1, day 1 if completed within 5 days. A complete physical exam, including height (screening only) and weight, neurologic assessment and assessment for lymphadenopathy/organomegaly will be conducted at screening, day one of each cycle, end

of treatment visit. A symptom directed physical examination will be conducted as needed during a cycle. Weight to be measured on day one of each cycle. Objective assessment of peripheral neuropathy as per CTCAE v 4.0 should be documented on Day 1 of every cycle of treatment.

2. Negative pregnancy test done at screening and ≤3 days (72 hours) prior to registration, for women of childbearing potential.
3. Standard of care procedure ≤28 days prior to registration, as clinically indicated after cycle 1, and to document CR or PD while on treatment.
4. Serum immunoglobulins to include IgA, IgG, IgM in all cases and IgD, IgE as clinically indicated.
5. Tumor measure will be done by physical examination and or biochemical testing of the blood (such as M spike, IgM levels). In addition, radiological evaluation can be used if clinically needed. The modality of radiological testing such as PET scan, or CT scan or MRI scan of the specific part of the body (i.e. chest or abdomen or pelvis) will be selected based upon the clinical needs or clinical scenario (i.e. site where extranodal / extramedullary disease was observed) of the patient and at the discretion of the treating physician. None of these scans is mandatory and will only be utilized to best assess patient disease consistent with standard clinical practice guidelines. It is recommended to use same measurement technique throughout the study to be consistent with assessing accurately the response to treatment. If imaging is the predominant method of assessing disease burden (such as in cases of extramedullary, or extranodal disease or hypo-secretory patient) then it is recommended to be done every 2 cycles or as clinically necessary to accurately and timely assess response (or lack of) to the treatment give. Every 2 months radiological testing is not mandatory for all patients. Note: PET scan is not mandatory in this study. If baseline PET scan is done as per clinical practice guidelines than it is recommended that a post end of treatment scan be done to assess response, however given the re-imbursement challenges of PET scan – this is not mandatory and will be done as part of standard of care and consistent with the best clinical practice.
6. To be performed at screening and as clinically indicated throughout the study. Check EKG at any time if the patient's vital signs suggest an issue or if the patient has complaints that could be related to atrial fibrillation as per the physician's assessment.
7. The diary must begin the day the patient starts taking the medication and must be completed per protocol and returned to the treating institution OR compliance must be documented in the medical record by any member of the care team.
8. Blood specimens will be collected and submitted as specified in Section 14.0. Kits are required.
9. UPEP testing required at baseline only. Subsequent testing will be as needed per physician discretion.
10. Collected at registration but prior to treatment
11. After Cycle 1, Additional samples to be drawn if a bone marrow is done for confirmation of response or as otherwise clinically indicated.
12. Patient return visit requirements: Day 1 of cycles 1, 2, 3 and 4. After cycle 4, the patient may be allowed to come every other cycle (to coincide with cycle 6, 8, 10, 12, 14, 16, 18, 20, 22, 24) if considered appropriate by the treating physician. (See section 7.3)

R Research funded (see Section 19.0)

4.2 Survival Follow-up

	Survival Follow-up[1]			
	Every 3 months until disease progression or subsequent treatment	At disease progression or initiation of subsequent therapy	Every 6 months after disease progression or initiation of subsequent therapy	At death
Event Monitoring	X	X	X	X

1. If a patient is still alive 5 years after registration, no further follow-up is required.

5.0 Stratification Factors OR Grouping Factor:

None.

6.0 Registration/Randomization Procedures

6.1 Registering a patient

To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the registration/randomization application. The registration/ randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the website. If unable to access the website, call the MCCC Registration Office at (507) 284-2753 between the hours of 8 a.m. and 5:00 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the MCCC web page (http://ccswww/training/index.html) and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and an MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the MCCC Registration Office (507) 284-2753. If the patient was fully registered, the MCCC Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to “Instructions for Remote Registration” in section “Finding/Displaying Information about A Registered Subject.”

6.2 Verification of information

Prior to accepting the registration, the registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient registration eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information.

6.3 Documentation of IRB approval

Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office (fax: 507-284-0885). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

6.4 Correlative Research

6.41 A mandatory correlative research component is part of this study, the patient will be automatically registered onto this component (see Sections 3.18, 14.1*)*.

6.5 Treatment on protocol

Treatment on this protocol must commence at Mayo Clinic Rochester or Mayo Clinic Florida under the supervision of a medical oncologist/hematologist.

6.6 Treatment start

Treatment cannot begin prior to registration and must begin ≤ 28 days after registration.

6.7 Pretreatment

Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.8 Baseline symptoms

All required baseline symptoms (see Section 10.6) must be documented and graded.

6.9 a Study drug

Study drug is available on site.

6.9b Blood draw kits

Blood draw kit is available on site.

6.9c Study Conduct

The clinical trial will be conducted in compliance with regulations (21 CFR 312, 50, and 56), guidelines for Good Clinical Practice (ICH Guidance E6), and in accordance with general ethical principles outlined in the Declaration of Helsinki; informed consent will be obtained from all participating patients; the protocol and any amendments will be subject to approval by the designated IRB prior to implementation, in accordance with 21 CFR 56.103(a); and subject records will be stored in a secure location and subject confidentiality will be maintained. The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

7.0 Protocol Treatment

Both the study drugs are to be self-administered by the patients. Ibrutunib is administered daily as 3 tablets and ixazomib is to be taken as per the schedule below. Ixazomib may be administered by the patient within ±1 day of the scheduled dose.

7.1 Treatment Schedule

Table 7.1a

Agent	Dose	Route	Day	Cycles*
Ixazomib	4 mg	PO	1, 8, 15	Cycle 1-24
Ibrutinib	420 mg	PO	1-28	Cycle 1-24

*All Cycles = 28 days each (except at treatment completion where cycle length will be the number of treatment days in that cycle + 28 days)
Any dose adjustments will be made as per guidelines in section 8.
Use actual weight or estimated dry weight if fluid retention

Treatment Schedule (in case of dose de-escalation required after safety analysis of first 6 patients as per Section 16.215)

Table 7.1b

Agent	Dose	Route	Day	Cycles*
Ixazomib	3 mg	PO	1, 8, 15	Cycle 1-24
Ibrutinib	420 mg	PO	1-28	Cycle 1-24

*All Cycles = 28 days each (except at treatment completion where cycle length will be the number of treatment days in that cycle + 28 days)
Any dose adjustments will be made as per guidelines in section 8.
Use actual weight or estimated dry weight if fluid retention

7.2 Treatment by local medical doctor (LMD)

Treatment by a local medical doctor (LMD) is not allowed.

7.3 Return to treating institution

For this protocol, the patient must return to the consenting institution for evaluation and drug administration at least every 28 days during treatment for the first 4 cycles. After cycle 4, patients may elect to return every other cycle per treating MD's discretion as long as there are no active ongoing toxicities that have not returned to baseline. Clinical evaluation and blood tests can be obtained per test schedule and mailed/faxed to the consenting institution and patient can return at least every other cycle for follow up to the consenting institution. The cycle length will remain at 28 days and data collection forms will be due at the end of each cycle. Adverse events and adherence to study treatment will be collected at the end of each cycle by telephone for cycles where the patient does not return to the clinic. The patient should retain the pill diaries and medication bottles (even if unopened or empty) along with any unused pills for each cycle and bring them to their next visit so that dosing can be recorded on the evaluation/treatment forms for each cycle.

8.0 Dosage Modification Based on Adverse Events

A dose of ixazomib and ibrutinib (as per attribution by the treating physician) is held if a patient experiences any of the following considered at least possibly related to ixazomib and/or ibrutinib at the beginning of a new cycle of treatment:

- ANC <1,000/mm3 (grade 2)
- Platelet <75,000/mm3 (grade 1)
- Any other nonhematologic toxicity (except for alopecia or fatigue) ≥ grade 3 with the

following considerations:

- Grade 3 nausea, vomiting or diarrhea will be considered significant if they occur despite appropriate maximal anti-emetic and/or antidiarrheal therapy.
- Grade 3 hyperglycemia will be a considered significant if the patient is symptomatic or glucose level is >300 mg/ml despite appropriate administration of insulin and/or oral antidiabetic agents.

→ ALERT: ADR reporting may be required for some adverse events (See Section 10.0) ←

8.1 Dose Levels (Based on Adverse Events in Tables 8.*2* and 8.3)

Dose Level	***Ixazomib***	***Ibrutinib***
Starting Dose	4.0 mg	420 mg
-1	3.0 mg	280 mg
-2	2.3 mg	140 mg
-3	Discontinue	Current dose

NOTE: If ixazomib is discontinued, the patient can continue on single-agent ibrutinib at the dose the patient is on when ixazomib is discontinued.

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) current version 4.0* unless otherwise specified ← ←

* Located at http:/ctep.cancer.gov/protocolDevelopment/electronic_applications.ctc.htm

8.2 Ixazomib dose modifications

CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
Investigations	Neutrophil count decreased Grade 4	Ixazomib	*Omit dose until AE has resolved to Grade 2 or better • Follow CBC weekly * If neutropenia has resolved to ≤Grade 2, resume dose at one level lower *If, after ixazomib has been omitted, and the AE does not return to ≤Grade 2within 4 weeks, then the patient may continue on single-agent ibrutinib till the completion of treatment and then proceed to survival follow-up
Blood and lymphatic system disorders	Febrile neutropenia ≥Grade 3		• Omit dose and follow CBC weekly • If neutropenia has resolved to ≤Grade 2, resume dose at same level with GCSF support (See Section 9.2)
Investigations	Platelet count decreased Grade 4		*Omit dose until AE has resolved to Grade 1 or better • Follow CBC weekly • If thrombocytopenia <25,000/mm^3 recurs, reduce dose by one dose level and continue therapy when platelet count ≥75,000/mm^3 If, after ixazomib has been omitted, and the AE does not return to ≤Grade 1 within 4 weeks, then the patient may continue on single-agent ibrutinib till the completion of treatment and then proceed to survival follow-up

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION**
Nervous System Disorders	Peripheral Motor Neuropathy and Peripheral Sensory Neuropathy.Grade 2 or Grade 1 with pain		Omit ixazomib until resolution to Grade ≤ 1 without pain or baseline. *If, after ixazomib has been omitted, and the AE does not return to ≤Grade 1 within 4 weeks, then the patient may continue on single-agent ibrutinib till the completion of treatment and then proceed to survival follow-up
	New or worsening Grade 2 peripheral motor neuropathy and peripheral sensory neuropathy with pain or Grade 3		Omit ixazomib until resolution to Grade ≤ 1 without pain or baseline and then reduce ixazomib to next lower dose upon recovery. *If, after ixazomib has been omitted, and the AE does not return to ≤Grade 1 within 4 weeks, then the patient may continue on single-agent ibrutinib till the completion of treatment and then proceed to survival follow-up.
	New or worsening Grade 4 peripheral neuropathy		Discontinue ixazomib. The patient may continue on single-agent ibrutinib till the completion of treatment and then proceed to survival follow-up.

** Use the following to describe actions in the Action column:

- **Omit** = The current dose(s) for the specified drug(s) during a cycle is skipped. The patient does not make up the omitted dose(s) at a later time.
- **Hold/Delay** = The current dose(s) of all drugs during a cycle is delayed. The patient does make up the delayed dose(s) when the patient meets the protocol criteria to restart drugs.
- **Discontinue** = The specified drug(s) are totally stopped.

Additional Adverse Events:

Grade ≥3 non-hematological toxicity (other than peripheral neuropathy) considered at least probably related to ixazomib:

- Omit ixazomib until resolution to Grade ≤ 1 or baseline, then restart at the same dose.
- If not recovered to ≤ Grade 1 or baseline despite adequate supportive care within 4 weeks, then the patient may continue on single-agent ibrutinib till the completion of treatment and then proceed to survival follow-up.
- For reoccurrence of ≥3 non-hematological toxicity (other than peripheral neuropathy) omit ixazomib until resolution to Grade ≤ 1 or baseline, then restart at one lower dose level.
- **For ≥3 nausea, vomiting or diarrhea:** Once the ixazomib is omitted and the toxicity recovers to Grade ≤ 1 or baseline within 4 weeks of holding ixazomib, it should be restarted at one lower dose level.
- Once ixazomib is reduced for any toxicity, the dose may not be re-escalated. If it is ultimately determined that therapy with ixazomib is no longer safe, the patient may continue on ibrutinib until completion of treatment and then proceed to survival follow.

- If multiple AEs are seen, administer the dose based on the greatest reduction required by any single AE observed. Dose modifications are for AEs attributed to study treatment only. Dose modifications are not required for AEs if they are deemed unlikely or unrelated to study treatment.

8.3 Ibrutinib dose modifications

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION**
Investigations	Neutrophil count decreased Grade 4	Ibrutinib	If the AE does not return to ≤Grade 2 after reduction of ixazomib to 2.3 mg, then reduce ibrutinib dose as per table 8.1. If no recovery on the 140 mg dose level, then discontinue study therapy and then proceed to survival follow-up.
Investigations	Platelet count decreased Grade 4		If the AE does not return to ≤Grade 1 after reduction of ixazomib to 2.3 mg, then reduce ibrutinib dose as per table 8.1. If no recovery on the 140 mg dose level, then discontinue study therapy and then proceed to survival follow-up.

** Use the following to describe actions in the Action column:

- **Omit** = The current dose(s) for the specified drug(s) during a cycle is skipped. The patient does not make up the omitted dose(s) at a later time.
- **Hold/Delay** = The current dose(s) of all drugs during a cycle is delayed. The patient does make up the delayed dose(s) when the patient meets the protocol criteria to restart drugs.
- **Discontinue** = The specified drug(s) are totally stopped.

Additional Adverse Events:

- The dose of ibrutinib will be omitted in case a patient experiences any of the following considered at least possibly related to ibrutinib:
  Any Grade ≥3 or greater non-hematological toxicities (other than alopecia or fatigue) with the following considerations:
  - Grade 3 nausea, vomiting or diarrhea will be considered significant if they occur despite appropriate maximal anti-emetic and/or antidiarrheal therapy.
  - Grade 3 hyperglycemia will be a considered significant if the patient is symptomatic or glucose level is >300 mg/ml despite appropriate administration of insulin and/or oral antidiabetic agents.
- Ibrutinib will be omitted until the non-hematologic AE recovers to Grade ≤1 or baseline and may be restarted at the original dose for the first occurrence.
- Upon each subsequent occurrence, ibrutinib is restarted at the next lower dose (as per Table 8.1) after recovery to Grade ≤1 or baseline.
- If Grade ≥3 non-hematological AE or Grade 4 neutropenia and thrombocytopenia occurs at the lowest dose, discontinue ibrutinib treatment. The treatment with ibrutinib should also be discontinued entirely if ibrutinib is omitted for 4 consecutive weeks or at the discretion of the Principal Investigator for patient safety. Patients may then continue with ixazomib monotherapy.
- Patient will discontinue ibrutinib and enter survival follow-up if AE is grade > 3 bleeding (other than bruising) that is probably or definitely attributed to ibrutinib.
- Patients who require a dose reduction during a given cycle will remain at that dose for at least 2 additional cycles. **At the investigator discretion, the dose of ibrutinib may be re-escalated after 2 cycles of a dose reduction in the absence of a recurrence of the toxicity that led to this reduction.**

This is particularly reasonable based upon the long-term safety data now available in Ibrutinib treated patients that show that most of the hematological or non-hematological AEs either decreased or remained stable.

If multiple AEs are seen, administer the dose based on the greatest reduction required by any single AE observed. Dose modifications are for AEs attributed to study treatment only. Dose modifications are not required for AEs if they are deemed unlikely or unrelated to study treatment.

9.0 Ancillary Treatment/Supportive Care

9.1 Full supportive care

Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.2 Blood products and growth factors

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the Journal of Clinical Oncology, Volume 33, No 28 (October 1), 2015: pp. 3199-3212 (WBC growth factors) AND Journal of Clinical Oncology, Volume 28, No 33 (November 20), 2010: pp. 4955-5010 (darbepoetin/epoetin).

9.3 Antiemetics

Antiemetics may be used at the discretion of the attending physician.

9.4 Diarrhea

Diarrhea could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).

In the event of Grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (Grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting **should be hospitalized** for intravenous hydration and correction of electrolyte imbalances.

9.5 Prior or Concomitant treatment:

- Ancillary treatments will be given as medically indicated; they should be recorded in the patient's medical chart and on the appropriate Case Report Form (CRF).
- Radiotherapy may be given concomitantly for control of bone pain BUT NOT for lesions considered due to disease progression. If possible, not all evaluable lesions should be included in the irradiated field. If this cannot be realized, the patient will be removed from the study and will not be evaluable for response from that moment on. Any lesion within the irradiated area cannot be used as a parameter for response assessment. The area should therefore be as small as possible.
- Patients will not receive other anticancer treatments or other investigational agents from start of study treatment until last study treatment. (Hormonal therapy for prior history of prostate or breast cancer are allowed).
- Due to potential of increased risk of viral infections, patients must be treated with antiviral prophylaxis starting Day 1 of treatment (e.g., acyclovir, valacyclovir or other).
- **For Ibrutinib:** Avoid co-administration with strong or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition. Concomitant use of strong CYP3A inhibitors which would be taken chronically (e.g., ritonavir, indinavir,

nelfinavir, saquinavir, boceprevir, telaprevir, nefazodone) is not recommended. For short-term use (treatment for 7 days or less) of strong CYP3A inhibitors (e.g., antifungals and antibiotics) consider interrupting ibrutinib therapy until the CYP3A inhibitor is no longer needed. Reduce ibrutinib dose to 140 mg if a moderate CYP3A inhibitor must be used (e.g., fluconazole, darunavir, erythromycin, diltiazem, atazanavir, aprepitant, amprenavir, fosamprevir, crizotinib, imatinib, verapamil, and ciprofloxacin). Patients taking concomitant strong or moderate CYP3A inhibitors should be monitored more closely for signs of ibrutinib toxicity. Any strong CYP3A inducers should be avoided concomitantly with ibrutinib (http://medicine.iupui.edu/clinpharm/ddis/main-table/). Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A. No dose adjustment is required in combination with mild inhibitors.

- **For Ixazomib:** Systemic treatment with any of the following metabolizing enzyme inducers should be avoided, unless there is no appropriate alternative medication for the patient's use: Strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital, and St. John's Wort).
- **Antiplatelet agents and anticoagulants:** Warfarin or vitamin K antagonist administration should be avoided concomitantly with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided. Use ibrutinib with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. Subjects requiring the initiation of therapeutic anticoagulation therapy (e.g., atrial fibrillation), consider the risks and benefits of continuing ibrutinib treatment. If therapeutic anticoagulation is clinically indicated, treatment with ibrutinib should be held and not be restarted until the subject is clinically stable and has no signs of bleeding. Subjects should be observed closely for signs and symptoms of bleeding. No dose reduction is required when study drug is restarted.

10.0 Adverse Event (AE) Monitoring and Reporting

The site principal investigator is responsible for reporting any/all serious adverse events to the sponsor as described within the protocol, regardless of attribution to study agent or treatment procedure.

The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

- Any suspected adverse reaction that is both serious and unexpected.
- Any findings from laboratory animal or *in vitro* testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug
- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).

Summary of SAE Reporting for this study
(please read entire section for specific instructions):

WHO:	WHAT form:	WHERE to send:
All sites	Pregnancy Reporting http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportFormUpdated.pdf	Mayo Sites – attach to MCCC Electronic SAE Reporting Form http://livecycle2.mayo.edu/workspace/?startEndpoint=MC4158-56/Processes/MC4158-56-Process.MC4158-56 Will automatically be sent to CANCERCROSAFETYIN@mayo.edu and RSTP2CSAES@mayo.edu Non Mayo sites – complete and forward to RSTP2CSAES@mayo.edu
Mayo Clinic Sites	Mayo Clinic Cancer Center SAE Reporting Form:http://livecycle2.mayo.edu/workspace/?startEndpoint=MC4158-56/Processes/MC4158-56-Process.MC4158-56 AND attach MedWatch 3500A: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf	Will automatically be sent to CANCERCROSAFETYIN@mayo.edu and RSTP2CSAES@mayo.edu

Definitions

Adverse Event
Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction
Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting
Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

Routine Reporting
Events reported to sponsor via case report forms

Events of Interest
Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

a. Identify the grade and severity of the event using the CTCAE version 4.0.
b. Determine whether the event is expected or unexpected (see Section 10.2).
c. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).
d. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).
e. Determine if other reporting is required (see Section 10.5).
f. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

NOTE: A severe AE is NOT the same as a serious AE, which is defined in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.
An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.
NOTE: *The consent form may contain study specific information at the discretion of the Principal Investigator; it is possible that this information may NOT be included in the protocol or the investigator brochure. Refer to protocol or IB for reporting needs.

10.3 Attribution to agent(s) or procedure

When assessing whether an adverse event (AE) is related to a medical agent(s) medical or procedure, the following attribution categories are utilized:

Definite - The AE *is clearly related* to the agent(s)/procedure.
Probable - The AE *is likely related* to the agent(s)/procedure.
Possible - The AE *may be related* to the agent(s)/procedure.
Unlikely - The AE *is doubtfully related* to the agent(s)/procedure.
Unrelated - The AE *is clearly NOT related* to the agent(s)/procedure.

10.31 AEs Experienced Utilizing Investigational Agents and Commercial Agent(s) on the SAME (Combination) Arm

NOTE: When a commercial agent(s) is (are) used on the same treatment arm as the investigational agent/intervention (also, investigational drug, biologic, cellular product, or other investigational therapy under an IND), the **entire combination (arm) is then considered an investigational intervention for reporting.**

- An AE that occurs on a combination study must be assessed in accordance with the guidelines for **investigational** agents/interventions.
- An AE that occurs prior to administration of the investigational agent/intervention must be assessed as specified in the protocol. In general, only Grade 4 and 5 AEs that are unexpected with at least possible attribution to the commercial agent require an expedited report, unless hospitalization is required. Refer to Section 10.4 for specific AE reporting requirements or exceptions.

An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.

- An increased incidence of an expected adverse event (AE) is based on the patients treated for this study at their site. A list of known/expected AEs is reported in the package insert or the literature, including AEs resulting from a drug overdose.
- Commercial agent expedited reports must be submitted to the FDA via MedWatch 3500A for Health Professionals (complete all three pages of the form).

  http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

10.32 EXPECTED Serious Adverse Events: Protocol Specific Exceptions to Expedited Reporting

For this protocol only, the following Adverse Events/Grades are expected to occur within this population and do not require Expedited Reporting. These events must still be reported via Routine Reporting (see Section 10.6).*

*Report any clinically important increase in the rate of a serious suspected adverse reaction (at your study site) over that which is listed in the protocol or investigator brochure as an expedited event.

*Report an expected event that is greater in severity or specificity than expected as an expedited event.

*Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event.

System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be reported in an expedited manner[1]
Blood and lymphatic system disorders	Anemia	≤Grade 4
Gastrointestinal	Vomiting	≤Grade 3
	Nausea	≤Grade 3
	Diarrhea	≤Grade 3
General disorders and administrations site conditions	Fatigue	≤Grade 3
Investigations	Lymphocyte count decreased	≤Grade 4
	Neutrophil count decreased	≤Grade 4
	Platelet count decreased	≤Grade 4
	White blood cell count decreased	≤Grade 4

[1] These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (*i.e.*, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for elective procedures unrelated to the current disease and/or treatment on this trial
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (*e.g.*, battery replacement) that was in place before study entry
- Hospitalization, or other serious outcomes for signs and symptoms of progression of the cancer.

10.4 Expedited Reporting Requirements for IND Agents

10.41 **Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND within 30 Days of the Last Administration of the Investigational Agent/Intervention** [1,2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the sponsor within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥24 hrs	7 Calendar Days	24-Hour 3 Calendar Days
Not resulting in Hospitalization ≥24 hrs	Not required	

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

10.42 General reporting instructions

The Mayo IND and/or MCCC Compliance will assist the sponsor-investigator in the processing of expedited adverse events and forwarding of suspected unexpected serious adverse reactions (SUSARs) to the FDA and IRB.

Use Mayo Expedited Event Report form http://livecycle2.mayo.edu/workspace/?startEndpoint=MC4158-56/Processes/MC4158-56-Process.MC4158-56 and US FDA MedWatch form

http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf for investigational agents or commercial/investigational agents on the same arm.

Site CRA to Contact (Takeda):
SAE and Pregnancy Reporting Contact Information
Fax Number: 1-800-963-6290
Email: TakedaOncoCases@cognizant.com
Suggested Reporting Form:

- SAE Report Form (provided by Takeda)
- US FDA MedWatch 3500A: http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm
- Any other form deemed appropriate by the sponsor-investigator

10.43 Reporting of re-occurring SAEs

ALL SERIOUS adverse events that meet the criteria outlined in table10.41 MUST be immediately reported to the sponsor within the timeframes detailed in the corresponding table. This reporting includes, but is not limited to SAEs that re-occur again after resolution.

10.5 Other Required Reporting

10.51 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS)

Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in general, include any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

Note: If there is no language in the protocol indicating that pregnancy is not considered an adverse experience for this trial, and if the consent form does not indicate that subjects should not get pregnant/impregnate others, then any pregnancy in a subject/patient or a male patient's partner (spontaneously reported) which occurs during the study or within 120 days of completing the study should be reported as a UPIRTSO.

Mayo Clinic Cancer Center (MCCC) Institutions:

If the event meets the criteria for IRB submission as a Reportable Event/UPIRTSO, provide the appropriate documentation and use the Mayo Clinic Cancer Center Expedited Event Report form http://livecycle2.mayo.edu/workspace/?startEndpoint=MC4158-56/Processes/MC4158-56-Process.MC4158-56, to submit to CANCERCROSAFETYIN@mayo.edu. The Mayo Clinic Compliance Unit will review and process the submission to the Mayo Clinic IRB and work with the IND Coordinator for submission to FDA.

10.52 Death

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND requires expedited reporting within 24-hours.

Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND requires expedited reporting within 24-hours.

Reportable categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (including cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.53 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
- All secondary malignancies that occur following treatment with an agent under an IND will be reported. Three options are available to describe the event:
  - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])
  - Myelodysplastic syndrome (MDS)

- Treatment-related secondary malignancy
- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.54 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting unless otherwise specified.

10.55 Pregnancy, Fetal Death, and Death Neonatal

If a female woman becomes pregnant or suspects that she is pregnant while participating in this study or within 90 days after the last dose, she must inform the investigator immediately and permanently discontinue study drug. The sponsor-investigator must immediately fax a completed Pregnancy Form to the Takeda Department of Pharmacovigilance or designee. 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 Takeda Department of Pharmacovigilance or designee (see Section 8.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Prior to obtaining private information about a pregnant woman and her infant, the investigator must obtain consent from the pregnant woman and the newborn infant's parent or legal guardian before any data collection can occur. A consent form will need to be submitted to the IRB for these patients if a pregnancy occurs. If informed consent is not obtained, no information may be collected.

In cases of fetal death, miscarriage or abortion, the mother is the patient. In cases where the child/fetus experiences an SAE other than fetal death, the child/fetus is the patient.

Suggested Pregnancy Reporting Form:

Pregnancy Report Form (provided by Takeda)

NOTE: When submitting Mayo Expedited Adverse Event Report reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section. Include any available medical documentation. Include this form:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportFormUpdated.pdf

10.551 Pregnancy

Pregnancy should be reported in an expedited manner as **Grade 3 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy)"** under the Pregnancy, puerperium and perinatal conditions SOC. Pregnancy should be followed until the outcome is known.

10.552 Fetal Death

Fetal death is defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of

respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation."

Any fetal death should be reported expeditiously, as **Grade 4 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy loss)"** under the Pregnancy, puerperium and perinatal conditions SOC.

10.553 Death Neonatal

Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention, should be reported expeditiously.

A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration - Other (neonatal loss)"** under the General disorders and administration SOC.

10.6 Required Routine Reporting

10.61 Baseline and Adverse Events Evaluations

Pretreatment symptoms/conditions to be graded at baseline and AEs to be graded at each evaluation.

Grading is per CTCAE v4.0 **unless** alternate grading is indicated in the table below:

System Organ Class	Adverse event/Symptoms	Baseline	Each evaluation
Blood and lymphatic system disorders	Anemia	X	X
Gastrointestinal disorders	# of stools	X	
	Diarrhea		X
	Nausea		X
	Vomiting		X
General disorders and administration site conditions	Fatigue	X	X
Investigations	Neutrophil count decreased	X	X
	Platelet count decreased	X	X
Nervous system disorders	Peripheral motor neuropathy	X	X
	Peripheral sensory neuropathy	X	X

10.62 Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient:

- Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.
- Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.
- Grade 5 AEs (Deaths)
- Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.
- Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.7 Late Occurring Adverse Events

Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

10.8 Takeda Additional Event Reporting Instructions

10.81 Special reporting requirements for **Takeda (Pharmaceutical Sponsor)**

Serious Adverse Event Definition

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

Results in death.

Is life-threatening (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).

Requires inpatient hospitalization or prolongation of an existing hospitalization (see clarification in the paragraph below on planned hospitalizations).

- Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).

Is a congenital anomaly/birth defect.

Is a medically important event. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term severe is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as serious, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

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

AEs which are serious must be reported to Takeda Pharmacovigilance (or designee) from the first dose of study drug through 30 days after administration of the last dose of Ixazomib. Any SAE that occurs at any time after completion of Ixazomib treatment or after the designated follow-up period that the sponsor-investigator and/or sub-investigator considers to be related to any study drug must be reported to Takeda 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 Takeda 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, Asher Chanan-Khan, MD, also referred to as the sponsor-investigator, is responsible for reporting serious adverse events (SAEs) to any regulatory agency and to the sponsor- investigator's EC or IRB.

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

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

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

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

The SAE report must include at minimum:
Event term(s)
Serious criteria

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

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

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

  In the event that this is a multisite study, the sponsor-investigator is responsible to ensure that the SAE reports are sent to Takeda 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 Takeda 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 Takeda 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.

10.82 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 Takeda and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Takeda Quality representative.

For Product Complaints

- Phone: 1-844-N1-POINT (1-844-617-6468)
- E-mail: GlobalOncologyMedinfo@takeda.com
- FAX: 1-800-881-6092
- Hours: Mon-Fri, 9 a.m. – 7 p.m. ET

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to Takeda Pharmacovigilance

11.0 Treatment Evaluation/Measurement of Effect

11.1 Terms and definitions

- **M-protein:** synonyms include M-spike, monoclonal protein and myeloma protein, paraprotein, M-component.

Serum M-protein level is quantitated using densitometry on SPEP except in cases where the SPEP is felt to be unreliable.

- M-proteins migrating in the β-region (usually IgA M-proteins)
- Cases in which the M-protein is so large and narrow on agarose (some specimens >4 g/dL) that they underestimate the actual immunoglobulin level (by greater than 1500 mg/dL) due to technical staining properties of the agarose gel.
- Cases in which there are multiple peaks of same M-protein (aggregates or dimers).

If SPEP is not available or felt to be unreliable (above examples) for routine M-protein quantitation, then quantitative immunoglobulin levels derived from nephelometry or turbidometry can be accepted, with the exception that quantitative IgG may not be used. However, this must be explicitly reported at baseline, and only nephelometry can be used for that patient to assess response. SPEP derived M-protein values and quantitative nephelometric immunoglobulin values cannot be used interchangeably.

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

- **FLC estimation** is currently carried out using the serum FLC assay (Freelite, The Binding Site Limited, UK). Patients with kappa/lambda FLC ratio <0.26 are defined as having monoclonal lambda FLC and those with ratios >1.65 as having a monoclonal kappa FLC. The monoclonal light chain isotype is considered the involved FLC isotype, and the opposite light chain type as the uninvolved FLC type.

Response terms: The following response terms will be used: complete response (CR), Very Good Partial Response (VGPR), Partial Response (PR), Minor Response (MR), Stable Disease (SD), and Progressive Disease (PD). (APPENDIX III)

An objective status of CR is defined as (See Appendix III):

- Absence of serum monoclonal IgM protein by immunofixation
- Normal serum IgM level
- Complete resolution of extramedullary disease, i.e. lymphadenopathy and splenomegaly if present at baseline
- Morphologically normal bone marrow aspirate and trephine biopsy (*ref: Owen 2013*)
- No signs or symptoms attributable to WM

12.0 Descriptive Factors

12.1 Prior ibrutinib treatment at the time of registration: yes vs. no.

13.0 Treatment/Follow–up Decision at Evaluation of Patient

Reason Off Treatment (from the Off Treatment Form)	***Go to CFU, SFU, or end folder rollout***
1 = Treatment (Intervention) Completed Per Protocol Criteria	CFU

2 = Patient Withdrawal/Refusal After Beginning Protocol Therapy (Intervention)	SFU
3 = Adverse Events/Side Effects/Complications	SFU
4 = Disease Progression, Relapse During Active Treatment (Intervention)	SFU
5 = Alternative Therapy	SFU
6 = Patient Off-Treatment (Intervention) For Other Complicating Disease	SFU
7 = Death On Study	No follow-up
8 = Other	SFU
10 = Disease Progression Before Active Treatment (Intervention)	No follow-up
24 = Patient Withdrawal/Refusal Prior To Beginning Protocol Therapy (Intervention)	No follow-up

13.1 Continuation of treatment

Patients who are CR, VGPR, PR, MR, or SD will continue treatment per protocol.

13.2 Progressive disease (PD)

Treatment may continue as per treatment schema until disease progression as long as the patient continues to respond and does not have any unacceptable toxicity. Patients who develop PD while receiving therapy will go to the survival follow-up phase.

13.3 Off protocol treatment

Patients who go off protocol treatment for the following reasons will go to the survival follow-up phase per Section 4.2:

- Progressive Waldenstrom's macroglobulinemia at any time on the clinical trial
- Patient requests to discontinue study treatment
- Patient develops an intercurrent illness that precludes further participation, or requires a prohibited concomitant treatment
- The Investigator withdraws the patient in the patient's best interests
- Administrative reasons (e.g., the patient is transferred to hospice care)
- An adverse event, which in the opinion of the Investigator, precludes further trial participation
- A dose omission of more than 28 days beyond the scheduled date of retreatment for ixazomib and ibrutinib

All attempts should be made to complete the End of Treatment procedures if a patient goes off treatment early.

13.4 Clinical follow-up

If the patient has achieved CR, VGPR, PR, MR, or SD after the completion of 24 cycles of study treatment, the patient will be observed every 3 months for 2 years. After the completion of clinical follow-up, the patient will go to survival follow-up per Section 4.2 of the protocol. If the patient has progressive disease or receives subsequent treatment for Waldenstrom macroglobulinemia at any time while in clinical follow-up, the patient will go directly to survival follow-up.

13.5 Ineligibles

A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will go directly to the event-monitoring phase of the study (or off study, if applicable).

- If the patient received treatment, all data up until the point of confirmation of

ineligibility must be submitted. Survival follow-up will be required per the protocol.

- If the patient never received treatment, on-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

13.6 Major violation

A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the survival follow-up phase of the study. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. Survival follow-up will be required per Section 4.2 of the protocol.

13.7 Cancel

A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

14.0 Body Fluid Biospecimens

14.1 Summary Table of Research Blood and Body Fluid Specimens to be collected for this Protocol

Research (Section for more information)	Specimen Purpose (check all that apply)	Mandatory or Optional	Blood or Body Fluid being Collected	Type of Collection Tube (color of tube top)	Volume to collect per tube (# of tubes to be collected)	Baseline	During course of treatment	End of Treatment	Process at site? (Yes or No)	Temperature Conditions for Storage /Shipping
BTK Signalosome	☒ Correlative ☐ Eligibility Confirmation ☐ Banking ☐ Other (specify)	Mandatory	Bone marrow aspirate	Green Top tube	5 mL (2)	Baseline/ after registration but prior to treatment	After cycle 1 and then as clinically indicated*	Confirmed disease progression	No	Refrigerate
Effect of treatment on microenvironment	☒ Correlative ☐ Eligibility Confirmation ☐ Banking ☐ Other (specify)	Mandatory	Bone marrow aspirate	Green Top tube	5 mL (1)	Baseline/after registration but prior to treatment	After cycle 1 and then as clinically indicated*	Confirmed disease progression	No	Refrigerate
Effect of treatment on microenvironment	☒ Correlative ☐ Eligibility Confirmation ☐ Banking ☐ Other (specify)	Mandatory	Peripheral Blood	Green Top tube	5 mL (2)	Baseline/ after registration but prior to treatment	End of every 3 cycles while patient continues on treatment**	Confirmed disease progression	No	Refrigerate

* Additional samples to be drawn if a bone marrow is done for confirmation of response or as otherwise clinically indicated.
**Additional samples to be drawn in-between every 3 cycles in case there is confirmed disease progression

14.2 Shipping and Handling

14.21 **Kits will be used for this study**.

14.211 Kits will be supplied by the Biospecimen Accessioning and Processing (BAP).

Mayo Biorepositories
BAP/PRC FLA 4500 San Pablo Rd
Campus Support Center 150
Jacksonville, FL 32224

14.212 The kit contains supplies and instructions for collecting, processing and shipping specimens.

14.213 Participating institutions may obtain kits by using the Supply Order Form and sending it to the email on the form. Because we are charged for all outgoing kits, a small, but sufficient, supply of the specimen collection kits should be ordered prior to patient entry. **Supply Order Forms must be filled in completely and legibly for quick processing.**

14.214 Kits will be sent via FedEx® Ground at no additional cost to the participating institutions. **Allow at least two weeks to receive the kits.**

14.215 Kits will not be sent via rush delivery service unless the participating institution provides their own Fed Ex® account number or alternate billing number for express mail. **Cost for rush delivery of kits will not be covered by the study.**

14.216 **All specimens must be collected and shipped Monday – Thursday ONLY.**

14.41 Shipping Specimens

1. Biological samples (ie, plasma) should be shipped refrigerate. Samples should be shipped only on Monday, Tuesday, or Wednesday, and at least 2 days prior to a national holiday, in order to minimize the possibility of samples in transit over a weekend or holiday. If duplicate samples are to be shipped, send SET 1 samples and await confirmation of arrival before shipping the duplicate SET 2 samples.

2. Before shipping, make sure the sample tubes are tightly sealed. Separate each subject's samples as follows:

3. Separate the duplicate SET 2 samples from the SET 1 samples.

4. Place SET 1 samples for each subject into self-sealing bag (eg, Ziploc®) containing additional absorbent material.

5. Using a permanent marker, write the 4-digit randomization sequence number, sample matrix (ie, plasma), analyte (Ixazomib), number of samples, and "SET 1" on each self-sealing bag.

6. Place the bags of individual subject's samples into a larger plastic bag so that samples are double bagged. Duplicate SET 2 samples should be returned to the refrigerator for storage. Repeat steps 3 through 6 above when preparing duplicate samples for shipment, except self-sealing bags should be marked "SET 2."

An inventory of individual samples should accompany each shipment and should include the Sponsor's name, study drug (ixazomib), protocol number (MC178B), investigator's name, sample type (ie, plasma), randomization sequence number, cycle, profile day and scheduled time point, and intended sample storage conditions. When duplicate SET 2 samples are being shipped, make a copy of the original SET 1 sample inventory and mark as "SET 2." Place the inventory paperwork into a large self-sealing bag. SET 1 samples will be shipped refrigerate, followed by shipment of duplicate SET 2 samples after SET 1 samples have been received by the analytical laboratory.

7. For sample packing, utilize refrigerate packs appropriately. Use wypall or other material to insulate the double-bagged samples from direct contact with the cool pack. Place the sample bundles into a cardboard box (or other suitable container) and fill the excess space with packing materials.

8. Place the inventory paperwork (in a large self-sealing bag) on top of the refrigerate pack in the styrofoam container. Place the lid on the styrofoam container and seal completely with strapping tape. Place the styrofoam container in a cardboard shipping carton and seal securely with strapping tape.

9. Mark the outside of shipping carton(s) with a tally number (eg, 1 of 5, 2 of 5).

10. Affix the appropriate address label to each shipping carton and ship to
Chanan-Khan laboratory
Attn: Aneel Paulus, M.D.
Griffin Building 164
4500 San Pablo Rd.
Jacksonville, FL 32224

14.3 Background and Methodology

14.22 *To determine the role of members of the BTK signalosome in achievement or lack thereof of response to ibrutinib and ixazomib:* The variability in extent of response to a therapeutic agent may suggest underlying adaptability of the WM clone through components of the BTK signalosome. Patients with B-cell malignancies treated with ibrutinib demonstrate upregulation of p-Akt and p-Erk (downstream mediators of BTK) in some (but not all) cases, suggesting that these pathways may contribute to survival of the malignant clone. It was also concluded in this work that these cells might not be dependent upon the proximal BTK pathways mediated apoptosis and thus, resistant to killing by ibrutinib. To address this question we will establish the profile of BTK signalosome for each patient through determination of the mRNA (RT-PCR/nanostring assay; whole exome sequencing (WES), transcriptome analysis) and protein expression (western blot analysis) of members of the BTK signaling pathway and look for associations between this and eventual response (or lack thereof) to the treatment. The said tests will be done analyzing the lymphoplasmacytic cells enriched from the bone marrow samples collected at baseline, and then at the time of disease progression. This will help explore mechanisms of acquired resistance to ibrutinib when used with ixazomib. We will also look for pAKT, pS6 and pERK as indirect pharmacodynamic biomarkers analyzed in patient's PBMC collected as a peripheral blood sample.

14.23 *To explore biologic effects of Ibrutinib and Ixazomib on microenvironment in WM and correlate with response to treatment:* In cancer redirection of host immunity from a predominant Th2 to Th1 response can deliver antitumor response. Ibrutinib can bind to ITK, a member of the TEC-kinase family, which mediates TCR signaling through PLCg, NFAT, NF-kappaB and MAPK. This results in activation and proliferation of CD8+ cells. Our hypothesis is that ibrutinib with ixazomib alters the Th2:Th1 balance in the blood and bone marrow microenvironment, skewing towards a more Th1 profile and this may translate into clinical efficacy. We further hypothesize that the robustness of the Th1 response will direct this combination's depth of response. We will assess this in bone marrow samples comparing the baseline sample to one collected after 1 cycle of treatment with ibrutinib and ixazomib using the MultiOmyx Tumor Infiltrating Lymphocytes panel for T helper (CD4+), Treg (FOXP3+), T cytotoxic (CD8+), B cells (CD20+), macrophage (CD68+), NK cells (CD56+), immunosuppression (PD-L1), CD138+, CD38+, ITK and BTK. Furthermore, BTK/ITK occupancy by Ibrutinib has been associated with response rates in other B-cell malignancies where this is an effective agent (CLL) but this has never been tested in WM. This assay will be performed to assess target coverage in bone marrow samples obtained from patients at the end of 1 cycle of treatment with Ibrutinib and Ixazomib. In addition, PBMC samples (2 ml of whole blood with heparin) from baseline and after 1 cycle of treatment will be assessed for:

- Th1 cells (live+, CD19-, CD3+, CD4+, CD8-, IFNg+)
- Th2 cells (live+, CD19-, CD3+, CD4+, CD8-, IL4+)
- Th17 cells (live+, CD19-, CD3+, CD4+, CD8-, IL17+)
- Treg cells (live+, CD19-, CD14-, CD3+, CD4+, CD25+, CD127-, FOXP3, CCR4+).

15.0 Drug Information

IND number (pending)

- Investigator brochure and Drug order contact:
  Takeda Pharmaceuticals International Co
  Rebecca Kaganov
  Phone: (617) 679-7138
  Email address: Rebecca.Kaganov@takeda.com

15.1 **Ixazomib** (MLN9708, Ninlaro®)

15.11 Background: Ixazomib (MLN9708) is a second-generation small molecule inhibitor of the 20S proteasome that is under development for the treatment of multiple myeloma, other plasma cell dyscrasias, nonhematologic malignancies, and pediatric acute lymphoblastic leukemia and lymphoma. Ixazomib (MLN2238) refers to the biologically active, boronic acid form of the drug substance, ixazomib citrate (MLN9708). The transition to MLN2238 occurs in any aqueos system.

15.12 **Formulation**: The ixazomib (MLN9708) capsule drug product formulation consists of drug substance, microcrystalline cellulose, talc, and magnesium stearate. Seven different capsule strengths are manufactured: 0.2, 0.5, 2.0, 2.3, 3.0, 4.0, and 5.5 mg; each capsule strength has a unique color. Dosage strength is stated as ixazomib (the active boronic acid). Ixazomib (MLN9708) capsules are individually packaged in blisters.

Matching placebo capsules have been manufactured for the 2.3, 3.0, 4.0, and 5.5 mg ixazomib (MLN9708) capsules. The placebo capsules contain microcrystalline cellulose, talc, and magnesium stearate and are identical in color and size to the corresponding active dose.

15.13 **Preparation, Storage**: Ixazomib capsules (0.2 mg, 0.5 mg, 2 mg), individually packaged in blisters, can be stored at 2ºC to 8ºC or “Do not store above 25°C. Do not freeze." Ixazomib capsules (2.3 mg, 3 mg, 4 mg, and 5.5 mg), individually packaged in blisters can be stored at “2°C - 8°C” or “Do not store above 30°C. Do not freeze."

Ixazomib that is dispensed to the patient for take-home dosing should remain in the blister packaging until the point of use. The investigative site is responsible for providing the medication to the patient in units that comprise the correct daily dose configurations. Capsules should remain in the blisters until the point of use. Ixazomib capsules must be administered as intact capsules and must not be opened or manipulated in any way. Comprehensive instructions should be provided to the patient in order to ensure compliance with dosing procedures. Patients will be instructed to store the medication in the refrigerator until the time of use. Reconciliation will occur accordingly when the patient returns for their next cycle of therapy. Any extremes in temperature should be reported as an excursion and will be managed on a case by case basis. Returned unused capsules should be discarded in a proper biohazard container.

Ixazomib is an anticancer drug. As with other potentially toxic compounds, caution should be exercised when handling ixazomib. It is recommended to wear gloves and protective garments during preparation when dispensed in clinic. Please refer to published guidelines regarding the proper handling and disposal of anticancer agents.

15.14 **Administration:** Ixazomib (MLN9708) capsules must be administered as intact capsules and are not intended to be opened or manipulated in any way. Capsules should be taken on an empty stomach with approximately 8 oz (1 cup) of water at least 1 hour before or at least 2 hours after food.

Ixazomib should not be taken if the patient has had a serious allergic reaction to boron or boron containing products.

Health care providers should instruct patients and caregivers that only one dose of ixazomib should be taken at a time, and only at the prescribed interval (e.g. one capsule, once a week, on Days 1,8, and 15 of a 28-day cycle). The importance of carefully following all dosage instructions should be discussed with patients starting treatment.

15.15 Pharmacokinetics Information

a) Absorption: After oral dosing, ixazomib is rapidly absorbed with a median T_{max} of 1 hour. The lack of a discernible relationship between BSA and ixazomib clearance over a relatively wide BSA range (1.4-2.6 m^2) indicates that total systemic exposure (AUC) following fixed dosing should be independent of the individual patient's BSA. The absolute oral bioavailability of ixazomib is ~58%. A high-fat meal decreased both the rate and extent of absorption. Therefore, ixazomib should be administered on an empty stomach.

b) Distribution: The steady state volume of distribution is large and is estimated to be 543 L.. Protein binding is 99% to plasma proteins and the extent of binding is not altered by severe renal impairment, moderate-severe hepatic impairment.

c) Metabolism: Metabolism is the primary route for elimination of ixazomib by both CYP and non-CYP enzymes. CYP3A4 and 1A2 comprise the major CYP isozymes that contribute to Ixazomib metabolism.

d) Excretion: The mean terminal half-life is 9.5 days. Renal elimination is a minor clearance pathway for ixazomib. Dosing adjustment is not required in patients with mild and moderate renal impairment in studies. However, in a dedicated renal impairment study (C16015), unbound AUC0-last was 38% higher in patients with severe renal impairment or end-stage renal disease (ESRD) requiring dialysis as compared to patients with normal renal function. Accordingly, a reduced starting dose of ixazomib is recommended in patients with severe renal impairment and ESRD requiring dialysis. Ixazomib is not dialyzable and therefore can be administered without regard to the timing of dialysis. Unbound systemic exposures of ixazomib are 27% higher in patients with moderate or severe hepatic impairment as compared to patients with normal hepatic function. A reduced starting dose of ixazomib is recommended for patients with moderate or severe hepatic impairment.

15.16 Potential Drug Interactions

The PK of ixazomib was similar with and without coadministration of

clarithromycin, a strong CYP3A inhibitor, and therefore no dose adjustment is necessary when ixazomib is administered with CYP3A inhibitors. In the population PK analysis, coadministration of strong CYP1A2 inhibitors did not affect ixazomib clearance. Thus, no dose adjustment is required for patients receiving strong CYP1A2 inhibitors. In a clinical rifampin DDI study, ixazomib C_{max} and $AUC_{0\text{-last}}$ were reduced in the presence of rifampin by approximately 54% and 74%, respectively. As a result, the coadministration of strong CYP3A inducers with ixazomib should be avoided. Ixazomib is neither a time-dependent nor reversible inhibitor of CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5,

therefore the potential for Ixazomib to produce DDIs via CYP isozyme inhibition is low. Ixazomib did not induce CYP1A2, CYP2B6, and CYP3A4/5 activity. The potential for ixazomib to cause DDIs with substrates or inhibitors of P-gp, BCRP, MRP2, MATE-1, MATE2-K, OCT2, OAT1, OAT3, and OATPs is low.

Pharmacokinetic parameters for ixazomib coadministered with lenalidomide and dexamethasone (LenDex) are like those observed when ixazomib is administered as a single agent. This suggests that there is no readily apparent effect of coadministration of LenDex on the clinical PK of ixazomib.

Ixazomib should not be taken if the patient has had a serious allergic reaction to boron or boron containing products.

15.17 Known Potential Adverse Events

See the current version of the Investigator's Brochure for more complete information including potential risks, as well as recommendations for clinical monitoring and medical management of toxicity. There are no human data available for potential effect of ixazomib on pregnancy or development of the embryo or fetus; however, embryo-fetal studies in animals have demonstrated that ixazomib has the potential to cause lethality.

Very common (≥10%): peripheral edema, skin rash, constipation, diarrhea, nausea, vomiting, neutropenia, thrombocytopenia, peripheral neuropathy, peripheral sensory neuropathy, back pain, eye disease, upper respiratory tract infection.

Common (≥1% to <10%): Herpes zoster, hepatic insufficiency, blurred vision, conjunctivitis, xerophthalmia, pneumonia ,

Uncommon (<1%) or case reports: cholestatic hepatitis, hepatocellular hepatitis, hepatotoxicity, liver steatosis, peripheral motor neuropathy, reversible posterior leukoencephalopathy syndrome, Stevens-Johnson syndrome, Sweet's syndrome, thrombotic thrombocytopenic purpura, transverse myelitis, tumor lysis syndrome, thrombotic microangiopathy

Herpes zoster – antiviral prophylaxis should be considered in patients being treated with Ixazomib to decrease the risk of herpes zoster reactivation.

Overdose – There is no known specific antidote for ixazomib overdose. Symptoms of overdose are generally consistent with the known risks of ixazomib and reports have been associated with serious adverse events such as nausea, aspiration pneumonia, multiple organ failure, and death. In the event of an overdose in blinded studies, study medication assignment should be unblinded immediately. The clinician should consider admitting the patient to the hospital for IV hydration, monitoring for adverse drug reactions, monitoring of vital signs, and appropriate supportive care. Gastric lavage may be considered, but it should be kept in mind that ixazomib absorption is rapid. Ixazomib is not readily dialyzable.

15.18 Special populations:

- **Geriatric Use:** Of the total number of subjects in clinical studies of NINLARO, 55% were 65 and over, while 17% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients,

but greater sensitivity of some older individuals cannot be ruled out.

- **Renal Impairment:** In patients with severe renal impairment or ESRD requiring dialysis, the mean AUC increased by 39% when compared to patients with normal renal function. Reduce the starting dose ofNINLARO

in patients with severe renal impairment or ESRD requiring dialysis. NINLARO is not dialyzable and therefore can be administered without regard to the timing of dialysis

- **Hepatic Impairment:** In patients with moderate or severe hepatic impairment, the mean AUC increased by 20% when compared to patients with normal hepatic function. Reduce the starting dose of NINLARO in patients with moderate or severe hepatic impairment

15.19 Drug procurement:

Investigational product will be supplied free of charge to trial participants by Millennium Pharmaceuticals, Inc.

15.20 Nursing guidelines:

15.201 Capsules must be administered intact and should not be opened or manipulated in any way. Additionally, capsules should remain in the blister packs until they are ready to be taken. It is recommended to wear gloves and protective garments during preparation when dispensed in clinic.

15.202 Capsules should be taken on an empty stomach (either 1 hour before or 2 hours after meals) with 8 oz. of water. Make sure that patients are instructed to take exactly as directed to avoid overdose.

15.203 Cytopenias have been observed. Monitor CBC w/diff . Instruct patient to report any signs or symptoms of infection or bleedning to the study team.

15.204 GI side effects have been seen (nausea, diarrhea, vomiting), treat symptomatically and monitor for effectiveness of intervention.

15.205 Rash has been seen. Rarely Steven Johnson syndrome (SJS) has been seen with this agent. Instruct patients to report any rash to study team.

15.206 Assess patients concomitant medications, including over the counter and supplements. Ixazomib is metabolized through both CYP and non-CYP enzymes, and drug to drug interactions exist. Instruct patients not to start any new medications or supplements without checking with the study team first.

15.207 Fatigue has been seen. Instruct patient in energy conserving lifestyle.

15.208 Insomnia can be seen. Treat symptomatically and monitor for effectiveness.

15.209a Patients who have had an allergic reaction to boron or boron containing products should not take Ixazomib.

15.209b The following rare but life threatening conditions have been seen with agent: CHF, liver failure, TTP, TLS, renal failure, bowel obstruction, and RPLS, transverse myelitis, progressive multifocal leukoencephalopathy. Monitor labs closely, instruct patient to

report any new or worsening symptoms to the study team and provide further assessment based on symptoms.

15.210 Monitor LFT's. Rarely hepatotoxicity has been seen.

15.2 Ibrutinib for Oral Administration (Imbruvica®)

15.21 **Background**: Ibrutinib is a potent and irreversible inhibitor of Bruton's tyrosine kinase (BTK), an integral component of the B-cell receptor (BCR) and cytokine receptor pathways. Constitutive activation of B-cell receptor signaling is important for survival of malignant B-cells; BTK inhibition results in decreased malignant B-cell proliferation and survival.

15.22 **Formulation**: Commercially available for oral administration as a capsule: 140mg.

15.23 **Preparation and storage**: Refer to package insert for complete dispensing instructions. Store capsules at room temperature between 20°C and 25°C (68°F and 77°F). Excursions are permitted between 15° and 30°C (59°F to 86°F. Keep in original container.

15.24 **Administration:** Refer to the treatment section for specific administration instructions. The manufacturer recommends ibrutinib should be taken with water at the same time every day. Swallow capsules whole; do not open, break, or chew the capsules. Maintain adequate hydration during treatment. Hazardous agent; use appropriate precautions for handling and disposal.

15.25 **Pharmacokinetic information**:
Distribution: ~10,000 L
Bioavailability: Administration with food increased the maximum concentration by ~2 to 4-fold and the AUC 2-fold (compared with overnight fasting). Administration under fasting conditions resulted in exposure of ~60% compared to when administered either 30 minutes before or after a meal, or 2 hours after a high-fat meal.
Protein binding: ~97%
Metabolism: Hepatic via CYP3A (major) and CYP2D6 (minor) to active metabolite PCI-45227
Half-life elimination: 4 to 6 hours
Time to peak: 1 to 2 hours
Excretion: Feces (80%; ~1% as unchanged drug); urine (<10%, as metabolites)

15.26 Potential Drug Interactions:

Metabolism Effects: Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A4/5. Avoid concomitant use of ibrutinib with any of the following: CYP3A4 inducers (strong), CYP3A4 inhibitors (strong or moderate) and herbs that are CYP3A4 inducers or inhibitors. The levels of ibrutinib may be increased by CYP3A4 inhibitors and decreased by CYP3A4 inducers (the active metabolite has inhibitory activity towards Bruton's tyrosine kinase that is approximately 15 times lower than that of ibrutinib).

Transport Effects: Ibrutinib is a P-glycoprotein/ABCB1 inhibitor and may increase the serum concentrations of: afatinib, bosutinib, brentuximab, colchicine, active metabolites of dabigatran etexilate, doxorubicin, edoxaban, everolimus, ledipasvir, naloxegol, pazopanib, prucalopride, rifaximin, rivaroxaban, silodosin, topotecan and vincristine.

Ibrutinib may enhance the adverse/toxic effect of clozapine, leflunomide, natalizumab, pimecrolimus, tofacitinib, tacrolimus, and live vaccines. It may also enhance the adverse/toxic effect of anticoagulants and agents with antiplatelet properties. Dipyrone may enhance the adverse/toxic effect of Ibrutinib.

Grapefruit juice and Seville oranges moderately inhibit 3A4 and may increase ibrutinib exposure.

15.27 **Known potential toxicities**: Consult the package insert for the most current and complete information.

Common known potential toxicities, >10%:
Cardiovascular: Peripheral edema, hypertension
Central nervous system: Fatigue, dizziness, headache, anxiety, chills
Dermatologic: Skin rash, skin infection, pruritis
Endocrine & metabolic: Hyperuricemia, hypoalbuminemia, hypokalemia, dehydration
Gastrointestinal: Diarrhea, nausea, constipation, abdominal pain, vomiting, decreased appetite, stomatitis, dyspepsia, gastroesophageal reflux disease, upper abdominal pain
Genitourinary: Urinary tract infection
Hematologic & oncologic: Decreased platelet count, bruise, neutropenia, decreased hemoglobin, petechia, malignant neoplasm (secondary)
Infection: infection
Neuromuscular & skeletal: Musculoskeletal pain, arthralgia, muscle spasm, weakness, arthropathy
Ophthalmic: Dry eye syndrome, increased lacrimation, blurred vision, decreased visual acuity

Respiratory: Upper respiratory tract infection, dyspnea, sinusitis, cough, oropharyngeal pain, pneumonia, epistaxis, bronchitis
Miscellaneous: Fever

Less common known potential toxicities, 1% - 10%:
Cardiovascular: Atrial fibrillation, atrial flutter

Renal: Increased serum creatinine

Limited to important or life threatening: Abnormal platelet aggregation, hepatic failure, hypersensitivity (includes anaphylactic shock, angioedema, urticaria), interstitial pulmonary disease, onychoclasis, pneumonia due to *Pneumocystis carinii*, pneumonitis, progressive multifocal leukoencephalopathy, renal failure, Stevens-Johnson syndrome, tumor lysis syndrome

15.28 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.29 **Nursing Guidelines:**

- There are numerous drug to drug interactions. Record all of patient's medications including OTC, and herbal use. Avoid concomitant use with agents as listed in section 15.16.
- Ibrutinib should be taken with water at approximately the same time each day and can be taken with or without food. Capsules should be swallowed whole.
- Patients should be instructed to avoid eating grapefruit (including juice) and Seville oranges while on ibrutinib.
- Peripheral edema is common. Instruct patients to report this to the study team.
- Gastrointestinal side effects are common (diarrhea, nausea, constipation, abdominal pain, vomiting, etc). Treat symptomatically and monitor for effectiveness of intervention.
- Monitor CBC w/diff. Instruct patients in energy conserving lifestyle (anemia) and to report any unusual bruising or bleeding and/or signs or symptoms of infection to study team.
- Arthralgias, myalgias, and muscle spasm can be seen. Treat symptomatically and monitor for effectiveness.
- Monitor renal function/uric acid levels, especially in patients who may be experiencing dehydration.
- Respiratory symptoms may include, cough, SOB, and URI. Instruct patients to report these symptoms to the study team.
- Rarely patients can experience secondary skin cancers. Instruct patients to report any new skin lesions to the study team.
- Rash can be seen. Instruct patient to report to study team.
- Cardiac arrhythmias have been seen with this agent including a-fib, atrial flutter and ventricular tachyarrhythmia's, some of which have led to death. Instruct patients who experience any palpitations, lightheadedness, syncope, or SOB to see medical care immediately. This is especially important in patients who have pre-existing cardiac issues.

16.0 Statistical Considerations and Methodology

16.1 Overview

This is a Phase II, single arm, open-label, study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of the combination of ibrutinib and ixazomib administered to patients with WM.

16.11 Primary Endpoint: The primary endpoint of this trial is the rate of complete response. A complete response is defined as an objective status of CR per Appendix III at any time, where confirmation of the complete response status is required on two consecutive evaluations with a second immunofixation before calling the patient a CR. All patients meeting the eligibility criteria, who have signed a consent form and have begun treatment, will be evaluable for response, unless they are determined to be a major violation.

16.2 Statistical Design

16.21 Decision Rule: The largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 5%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 20%. The following one–stage design with an interim analysis is based on a two-stage Simon optimum design and requires 37 evaluable patients to test the null hypothesis that the true success proportion in this patient population is at most 5%.

16.211 Interim Analysis: Enter 12 evaluable patients into the study. If no successes are observed in the first 12 evaluable patients, we will consider this regimen ineffective in this patient population and terminate the study. Otherwise, if the number of successes is at least 1, we will continue accrual.

16.212 Final Decision Rule: Enter an additional 25 evaluable patients into the study. If 3 or fewer successes are observed in the first 37 evaluable patients, we will consider this regimen ineffective in this patient population and terminate this study. Otherwise, if the number of successes is at least 4, this will be considered evidence of promising activity and the treatment may be recommended for further testing in subsequent studies in this population.

16.213 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making process. Analyses involving over accrued patients are discussed in Section 16.313.

16.214 NOTE: We will not suspend accrual at the interim analysis to allow the first 12 patients to become evaluable, unless undue toxicity is observed. Given the limited overall sample size and the inclusion of an AE stopping rule, we feel it is ethical to not halt accrual for the interim analysis. However, if accrual is extremely rapid, we may temporarily suspend accrual in order to obtain safety data on these patients before re- opening accrual to further patients.

16.215 Dose de-escalation in safety analysis: A safety analysis will be performed in the first 6 evaluable patients per Section 16.4. In the case of unacceptable toxicity, the dose of ixazomib will be de-escalated (Table 7.1b). If this occurs, the first 6 patients will be evaluated separately and will not be included in any decision making criteria.

16.22 Sample Size: The one stage study design with an interim analysis to be utilized is fully described above. A minimum of 12 and a maximum of 37 evaluable patients will be accrued onto this phase II study unless undue toxicity is encountered. If dose de-escalation is required during the safety analysis, an additional 6 evaluable patients will be accrued per Section 16.4. We anticipate accruing an additional up to 4 patients to account for ineligibility, cancellation, major treatment violation, or other reasons for a total of up to 47 patients.

16.23 Accrual Rate and Study Duration: The anticipated accrual rate is 2 evaluable patients per month. At this rate, it will likely take about 2 years to enroll all patients. The maximum study duration is expected to be approximately 7 years, or until the last patient accrued has been followed by 5 years.

16.24 Power and Significance Level: Power and Significance Level: Assuming that the number of successes is binomially distributed, the significance level is .09, i.e. there is a 9% chance of finding the drug to be effective when it truly is not. The probability of declaring that this regimen warrants further study (i.e. statistical power) and the probability of stopping at the interim analysis under various success proportions can be tabulated as a function of the true success proportion as shown in the following table.

If the true success proportion is...	0.05	0.10	0.15	0.20
Then the probability of declaring that the regimen warrants further study is…	0.09	0.45	0.75	0.90
And the probability of stopping at the interim analysis is…	0.54	0.28	0.14	0.07

16.25 Other Considerations: AEs, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study

16.3 Analysis Plan

The analysis for this trial will commence at planned time points (see 16.2) and at the time the patients have become evaluable for the primary endpoint. The Statistician and Study Chair will make the decision, in accord with CCS Standard Operating Procedures, availability of data for secondary endpoints (e.g., laboratory correlates), and the level of data maturity. It is anticipated that the earliest date in which the results will be made available via manuscript, abstract, or presentation format is when last patient has been followed for at least 6 months.

16.31 Primary Outcome Analysis

16.311 Definition: The primary endpoint of this trial is the complete response rate. A success is defined as an objective status of CR per Appendix III at any time, where confirmation of the complete response status is required on two consecutive evaluations with a second immunofixation before calling the patient a CR. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response, unless they are determined to be a major violation.

16.312 Estimation: The proportion of successes will be estimated by the number of successes divided by the total number of evaluable patients. 95% confidence intervals for the true success proportion will be calculated according to the approach of Duffy and Santner.

16.313 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making processes; however, they will be included in final point estimates and confidence intervals.

16.32 Secondary Outcome Analysis

16.321 The overall response rate will be estimated by the total number of patients who achieve a CR VGPR, or PR divided by the total number of evaluable patients. All evaluable patients will be used for this analysis. Exact binomial 95% confidence intervals for the true overall response rate will be calculated.

16.322 Time to progression is defined as the time from registration to the earliest date of documentation of disease progression. The distribution of time to progression will be estimated using the method of Kaplan-Meier.

16.323 Overall survival is defined as the time from registration to death due to any cause. The distribution of overall survival will be estimated using the method of Kaplan-Meier.

16.324 AEs: All eligible patients that have initiated treatment will be considered evaluable for assessing AE rate(s). The maximum grade for each type of AE will be recorded for each patient, and frequency tables will be reviewed to determine patterns. Additionally, the relationship of the AE(s) to the study treatment will be taken into consideration.

16.33 Correlative Analysis

16.331 BTK signaling proteins (western blot and densitometric quantification) and gene expression (quantitative real-time PCR) will be examined in CD19/CD138+ WM cells collected from patients on the study. 15 protein/genes associated with BTK-signaling will be assessed and their levels from baseline samples will be compared with levels from samples during treatment. Changes over time will be evaluated using paired

sample approaches (Wilcoxon signed rank test). Baseline levels will be correlated with response (responder vs. non-responder) using Wilcoxon rank sum tests.

16.332 Exploration of the biologic effects of ibrutinib and ixazomib on microenvironment in WM will include 3 types of data:

- Immunophenotyping of tumor infiltrating lymphocytes (TILs) using the Multi-Omyx TILs platform. This will identify 17 different types of TILs from BM samples collected at baseline and then after one cycle of treatment. This data is represented as % and actual cell counts.
- Identification of 4 types of T-cells from the blood. This will be done from peripheral blood samples collected at Baseline and then after one cycle of treatment with Ixa+Ibr.
- BTK receptor occupancy: This is a competitive-binding assay essentially and will be performed in CD19+/CD138+ WM cells collected at baseline and then after one cycle of treatment with Ixa+Ibr. Readout is % occupancy

Values will be correlated with response (responder vs. non-responder) using Wilcoxon rank sum tests.

16.4 Early Safety Analysis

7.1 An early safety analysis will be performed after the first 6 evaluable patients have been accrued to the study and observed for one cycle. Accrual will be temporarily halted while these patients are evaluated. If 2 or more of the first 6 patients experience a significant toxicity as defined below, then the dose of ixazomib may be de-escalated (as per Table b). In this case, another safety analysis will be conducted on the first 6 evaluable patients treated at the reduced dose level.

Toxicity will be measured per NCI-CTCAE version 4. Significant toxicity is defined as an adverse event occurring during the first cycle of treatment that is possibly, probably, or definitely related to study treatment and that meets one of the following:

- Grade 3 diarrhea, nausea, and fatigue lasting > 3 days despite optimal supportive medications
- Any other ≥ Grade 3 non-hematological toxicity with the exceptions of electrolyte abnormalities that are reversible and asymptomatic.
- Febrile neutropenia
- Grade 3 thrombocytopenia with clinically significant bleeding
- Any ≥Grade 4 neutrophil count decreased or platelet count decreased that persists >7 days

16.5 Data & Safety Monitoring

16.51 The principal investigator(s) and the study statistician will review the study at least twice a year to identify accrual, AE, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.52 Adverse Event Stopping Rules
The stopping rules specified below are based on the knowledge available at study development. We note that the AE Stopping Rule may be adjusted in the event of

either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the AE profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected AE profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e. an AE with attribute specified as "possible," "probable," or "definite") that satisfy one of the following:

- if 4 or more patients in the first 12 treated patients experience a grade 4 or higher non-hematologic AE at least possibly related to treatment.
- if after the first 12 patients have been treated, 30% of all patients experience a grade 4 or higher non-hematologic AE at least possibly related to treatment.

We note that we will review grade 4 and 5 AEs deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related AE.

16.6 Results Reporting on ClinicalTrials.gov

At study activation, this study will have been registered within the "ClinicalTrails.gov" website. The Primary and Secondary Endpoints along with other required information for this study will be reported on www.ClinicalTrials.gov. For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this

study is 4 years after the study opens to accrual. The definition of "Primary Endpoint Completion Date" (PECD) for this study is at the time all patients registered have completed 24 cycles of treatment or have discontinued treatment before the completion of 24 cycles.

16.7 Subset Analyses for Minorities

16.71 Study availability

This study will be available to all eligible patients, regardless of gender, race or ethnic origin.

16.72 Statistical analysis by subset

There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.73 Regional population

The geographical region served by MCCC has a population which includes approximately 3% minorities. Based on prior MCCC studies involving similar disease sites, we expect about 3-5% of patients will be classified as minorities by race and about 20% of patients will be women.

Accrual Estimates by Gender/Ethnicity/Race

Ethnic Category	**Sex/Gender**			
	Females	**Males**	**Unknown**	**Total**
Hispanic or Latino	0	1	0	1
Not Hispanic or Latino	9	37	0	46
Ethnic Category: Total of all patients*	9	38	0	**47**
Racial Category				
American Indian or Alaskan Native	0	0	0	0
Asian	0	0	0	0
Black or African American	0	1	0	1
Native Hawaiian or other Pacific Islander	0	0	0	0
White	9	37	0	46
Racial Category: Total of all patients*	9	38	0	**47**

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens

17.1 None.

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Data submission instructions for this study can be found in the Data Submission Schedule.

18.2 Survival Follow-up

See Section 4.2

18.3 CRF completion

This study will use Medidata Rave for remote data capture (rdc) of all study data. Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active account and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the organization roster at the enrolling site.

18.4 Site responsibilities

Each site will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.5 Supporting documentation

This study requires supporting documentation for diagnosis, response to previous treatment with ibrutinib, and last date of ibrutinib treatment prior to study entry as well as for evidence of response to study therapy and progression after study therapy. Supporting documentation for diagnosis will include a pathology report and a laboratory report demonstrating Waldenström macroglobulinemia (including serum quantitative immunoglobulins, SPEP, UPEP, FLC, Serum and Urine Immunofixation, Bone Marrow Biopsy and Aspirate, CT/PET scan,). These reports should be uploaded into the Supporting Documentation: Baseline form within 14 days of registration.

For response to treatment, supporting documentation may include serum quantitative immunoglobulins, SPEP, UPEP, FLC, Serum and Urine Immunofixation, Bone Marrow Biopsy and aspirate, and PET scan. These documents should be uploaded into the Supporting Documentation form.

For patients who progress after study therapy supporting documentation may include any of the following: serum quantitative immunoglobulins, SPEP, UPEP, FLC, serum and urine immunofixation, bone marrow biopsy and aspirate, and PET/CT scan. These documents should be uploaded into the Supporting Documentation form

18.6 Labeling of materials

Each site will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.7 Overdue lists

A list of overdue forms and outstanding queries will be available in Rave through the Rave Task Summary. In addition to this, the Overdue Materials report is available on the Cancer Center Systems homepage.

19.0 Budget

19.1 Costs charged to patient: routine clinical care, ibrutinib

19.2 Tests to be research funded: ixazomib is provided by Takeda (Millennium) Pharmaceuticals, Inc, Bone Marrow Biopsy aspirate at Cycle 2 Day 1, personnel effort, statistics, and research correlatives.

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Appendix I ECOG Performance Status

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead

*As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

The ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

From http://www.ecog.org/general/perf_stat.html

Appendix II Patient Medication Diary

Name _____ Study ID Number _____

Please complete this diary on a daily basis. Please bring your dosing diary to your next scheduled appointment. Write in the amount of the dose of ixazomib and ibrutinib that you took in the appropriate "Day" box. On the days that you do not take any study drug, please write in "0". If you forget to take your daily dose, please write in "0" and do not make up this missed dose. Remember to take your prescribed dose at the next regularly scheduled time.

Please store the ixazomib as indicated on the bottle. Ixazomib should be taken on an empty stomach (either 1 hour before or 2 hours after meals) with 8 oz. of water. Swallow the capsules whole; do not open, break, or chew the capsules. If you experience a vomiting episode in the same day after taking ixazomib, do not make up this dose. Please indicate the time you took the drug and the time you vomited.

Ibrutinib should be taken with water at approximately the same time each day and can be taken with or without food. Swallow the capsules whole; do not open, break, or chew the capsules. Please avoid grapefruit and Seville oranges during your ibrutinib treatment. Supplements such as fish oil and vitamin E preparations should also be avoided.

If you experience any health/medical complaints or take any medication other than ixazomib and ibrutinib please record this information.

Study Drug(s)	**Dose**	**Study Coordinator only:** Write in the dose assigned by the study doctor in this column if different than the dose listed in the previous column
Ibrutinib	420 mg	
Ixazomib	4mg	

Week of:

Study Drug	***Day 1***	***Day 2***	***Day 3***	***Day 4***	***Day 5***	***Day 6***	***Day 7***
Date							
Ixazomib							
Ibrutinib							

Week of:

Study Drug	***Day 8***	***Day 9***	***Day 10***	***Day 11***	***Day 12***	***Day 13***	***Day 14***
Ixazomib							
Ibrutinib							

Week of:

Study Drug	***Day 15***	***Day 16***	***Day 17***	***Day 18***	***Day 19***	***Day 20***	***Day 21***
Ixazomib							
Ibrutinib							

Week of:

Study Drug	***Day 22***	***Day 23***	***Day 24***	***Day 25***	***Day 26***	***Day 27***	***Day 28***

Ixazomib							
Ibrutinib							

Patient signature: _____

Health or medical complaints during this time:

Other medications or supplements taken during this time:

Name of medication or supplement	How much did you take? (example: Two 500mg pills)	When did you take it (examples: Every day Or Day 19 and Day 20)

Use a separate sheet of paper if more space is needed.

My next scheduled visit is: _____

If you have any questions, please call: _____

Study Coordinator Use Only

Number of pills returned _____ Number of vials returned: _____

Discrepancy Yes____/No____ Verified by _____ Date_____

Appendix III Response Assessment Criteria

Response	Criteria
Complete response	• Absence of serum monoclonal IgM protein by immunofixation • Normal serum IgM level • Complete resolution of extramedullary disease, i.e., lymphadenopathy (resolution to ≤1.5 cm in longest diameter of all nodes) and splenomegaly/hepatomegaly if present at baseline • Morphologically normal bone marrow aspirate and trephine biopsy • No signs or symptoms attributable to WM Confirmation of the complete response status is required on two consecutive evaluations with a second immunofixation before reporting an objective status of CR
Very good partial response	• Monoclonal IgM protein is detectable • ≥90% reduction in serum IgM level from baseline • Complete resolution of extramedullary disease, i.e., lymphadenopathy (resolution to ≤1.5 cm in longest diameter of all nodes) and splenomegaly/hepatomegaly if present at baseline • No new signs or symptoms of active disease
Partial response	• Monoclonal IgM protein is detectable • ≥50% but <90% reduction in serum IgM level from baseline • ≥50% reduction in extramedullary disease, i.e., ≥50% reduction in SPD from baseline for lymphadenopathy and ≥50% reduction from baseline in splenomegaly/hepatomegaly if present at baseline • No new signs or symptoms of active disease
Minor response	• Monoclonal IgM protein is detectable • ≥25% but<50% reduction in serum IgM level from baseline • No new signs or symptoms of active disease
Stable disease	• Monoclonal IgM protein is detectable • <25% reduction and <25% increase in serum IgM level from baseline • No progression in extramedullary disease, i.e.,lymphadenopathy/splenomegaly/hepatomegaly • No new signs or symptoms of active disease
Progressive disease [1]	• ≥25% increase in serum IgM level from lowest nadir confirmed by a second measurement 4 weeks apart and/or progression in clinical features attributable the disease (i.e., anemia, thrombocytopenia, leukopenia, bulky adenopathy/ organomegaly)[2] or • symptoms attributable to WM (unexplained recurrent fever ≥38.4°C, drenching night sweats, ≥10% body weight loss, hyperviscosity, neuropathy, symptomatic cryoglobulinemia, or amyloidosis) or • Transformation to a more aggressive histology or • Progression criteria for lymphadenopathy: In patients who **achieved PR, MR, or SD** an increase of ≥ 25% from the nadir in the SPD of any previous lymph nodes or appearance of a new lymph node (that must be >

2 cm). For patients who have **achieved a VGPR or CR**, progression will be defined as appearance of a new lymph node (that must be ≥ 2 cm).

- Progression criteria based upon splenic or hepatic enlargement: In patients who **achieved PR, MR, or SD** an increase in the size of the spleen and / or liver of ≥ 25% from the nadir. For patients who have **achieved a VGPR or CR**, progression will be defined if there is increase in the size of spleen and / or liver that is ≥25% the upper limit of normal measured in the longitudinal axis.

[1] In the case where progression is first observed, the objective status will be entered as unconfirmed progression (uPD) on the measurement form. Once this criterion is confirmed at least 4 weeks later, the objective status will be entered as PD. If confirmed, the date of first evidence of progression (date of first uPD) will be considered the progression date (and should be entered on the event monitoring form).

[2] If IgM alone is used to determine progression, there must be ≥ 500 mg/dL increase in IgM from the nadir. (Owen, 2013)