PrECOG Protocol Number: PrE0404

A Phase I/II Study of Ixazomib and Ibrutinib in Relapsed/Refractory Mantle Cell Lymphoma

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A Phase I/II Study of Ixazomib and Ibrutinib in Relapsed/Refractory Mantle Cell Lymphoma

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Brief Protocol Synopsis

See Protocol Document Sections for complete details

Study Schema

Phase I

Open to Ibrutinib-Naïve and Selected Pretreated Patients →

Dose Level	Ixazomib Days 1, 8, 15 of a 28 Day Cycle	Ibrutinib Days 1-28 of a 28 Day Cycle
-1	3 mg	420 mg
1 **Starting Dose**	3 mg	560 mg
2	4 mg	560 mg

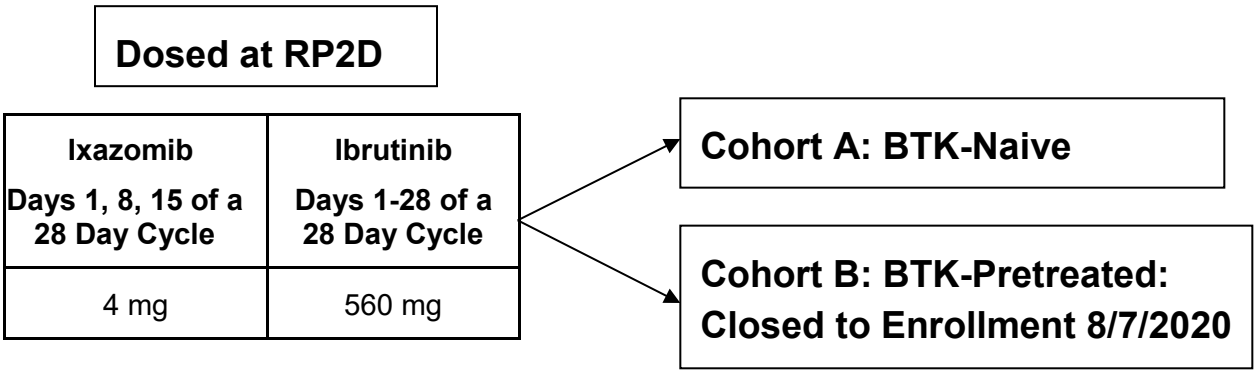
Phase I: Treatment should begin within 10 working days of registration.

Phase I: Dose Limiting Toxicity (DLT) will be assessed through Cycle 1. Refer to Section 6.2.1 for details.

Phase I Accrual: Maximum of 12 patients.

Three patients were enrolled to Dose Level 1 with no DLTs during the 28 day assessment period. Nine patients were enrolled to Dose Level 2, five of the nine patients completed the 28 day assessment period with no DLTs, and one patient experienced a Grade 3 lung infection that was considered a DLT. Three of the nine patients were not evaluable for DLT and were replaced. One patient was inadvertently given neulasta prior to receiving Cycle 2, Day 1 therapy; another patient unintentionally took Day 15 ixazomib on Day 9; and one patient forgot to take ibrutinib the last 8 days of Cycle 1 unrelated to any toxicities. Phase I was completed November 25, 2019. Dose Level 2 is the recommended Phase 2 dose.

Phase II



RP2D: Recommended Phase 2 Dose

BTK: Bruton's Tyrosine Kinase

Phase II: Treatment should begin within 10 working days of registration.

Phase II Accrual Goal: Maximum of 72 patients enrolled for 62 eligible, treated patients. **August 7, 2020:** Cohort A will continue to enroll patients (see below) and enrollment to Cohort B is closed.

Cohort A: 31 eligible, treated patients will be accrued (see below).

Cohort B: 31 eligible, treated patients will be accrued. **Closed to enrollment August 7, 2020**. Two patients enrolled.

August 7, 2020: Phase II opened December 17, 2019 with Cohort A: BTK-naïve or Cohort B: BTK-pretreated.

Enrollment to Cohort A: BTK-naïve will continue. We plan to reach our original accrual goal of 36 BTK-naïve subjects treated at the established Dose Level 2 for 31 eligible, treated patients. The Phase I BTK-naïve patients treated at Dose Level 2 will be included in the 36 patient total. Seventeen additional BTK-naïve patients will be enrolled to complete this cohort.

Enrollment to Cohort B: BTK-pretreated will close. To date, only two patients have enrolled in Cohort B.

List of Abbreviations

Abbreviation	Term
5-HT_3	5-Hydroxytryptamine 3 Serotonin Receptor
ADL	Activities of Daily Living
ADME	Absorption, Distribution, Metabolism, and Excretion
AE	Adverse Event
AL	Light-Chain Amyloidosis
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
ASCT	Autologous Stem Cell Transplant
AST	Aspartate Aminotransferase
AUC	Area Under the Plasma Concentration versus Time Curve
BCR	B-Cell Receptor
BCRP	Breast Cancer Resistance Protein
BM	Bone Marrow
BSA	Body Surface Area
BTK	Bruton's Tyrosine Kinase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CI	Confidence Interval
C_{max}	Maximum (peak) Concentration
CNS	Central Nervous System
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P_{450}
DDI	Drug-Drug Interaction
DLT	Dose-Limiting Toxicity
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form

Abbreviation	Term
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FFPE	Formalin-Fixed, Paraffin-Embedded
FISH	Fluorescence In Situ Hybridization
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
GI	Gastrointestinal
GM-CSF	Granulocyte Macrophage-Colony Stimulating Factor
GVHD	Graft-Versus-Host Disease
HIPAA	Health Information Portability and Accountability Act
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IHC	ImmunoHistoChemistry
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous; Intravenously
KPS	Karnofsky Performance Status
LDH	Lactate Dehydrogenase
LenDex	Lenalidomide plus Dexamethasone
MCL	Mantle Cell Lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
MM	Multiple Myeloma
MRI	Magnetic Resonance Imaging
MRP2	Multidrug Resistance Associated Protein 2
MTD	Maximum Tolerated Dose
N	Number
NCDB	National Cancer Data Base
NCI	National Cancer Institute

Abbreviation	Term
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDMM	Newly Diagnosed Multiple Myeloma
NEC	Not Elsewhere Classified
NHL	Non-Hodgkin's Lymphoma
NIH	National Institutes of Health
ORR	Overall Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PCR	Polymerase Chain Reaction
PD	Progressive Disease (disease progression)
PET	Positron Emission Tomography
PFS	Progression Free Survival
Pgp	P-Glycoprotein
PK	Pharmacokinetic(s)
PML	Progressive Multifocal Leukoencephalopathy
PO	*per os*; By Mouth (orally)
PR	Partial Response
PT	Partial Thromboplastin Time
RevDex	Revlimid plus Dexamethasone
RP2D	Recommended Phase 2 Dose
RRAL	Relapsed and/or Refractory Systemic Light Chain (AL) Amyloidosis
RRMM	Relapsed and/or Refractory Multiple Myeloma
SAE	Serious Adverse Event
SD	Stable Disease
SPD	Sum of the Product of the Diameters
SRM	Study Reference Manual
TEAE	Treatment-Emergent Adverse Event
TEN	Toxic Epidermal Necrolysis
T_{max}	Single-Dose Time to Reach Maximum (peak) Concentration
TNFα	Tumor Necrosis Factor-alpha
TTP	Thrombotic Thrombocytopenic Purpura
ULN	Upper Limit of the Normal Range

Abbreviation	Term
US	United States
WBC	White Blood Cell

1. Introduction- Background and Rationale

1.1 Mantle Cell Lymphoma – Disease Overview

Mantle cell lymphoma (MCL) is a rare subtype of non-Hodgkin lymphoma that is considered incurable with conventional therapy. The disease is identified through a characteristic chromosomal translocation [i.e., t(11;14)] which results in overexpression of cyclin D1. While patients who receive aggressive induction therapy followed by autologous stem cell transplant (ASCT) can have a prolonged overall survival (OS), ASCT is not considered curative and the OS for all diagnosed patients has not changed over the past several years (Figure 1). Current approaches to induction therapy for fit patients includes aggressive inpatient chemotherapy regimens followed by ASCT, which can result in responses of 5-8 years in many patients and prolonged OS.[1-3]

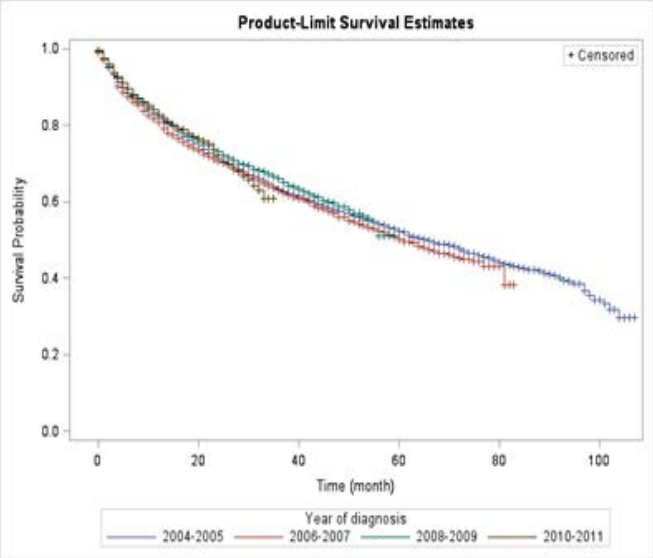


Figure 1. Overall survival (OS) of newly diagnosed patients with mantle cell lymphoma in the United States, based on time of diagnosis. Source: National Cancer Data Base (NCDB).

For relapsed patients, ibrutinib, lenalidomide, and bortezomib are all Food and Drug Administration (FDA)-approved options, although these do not represent curative approaches.[4-6] While ibrutinib has a high overall response rate (ORR) of 67% in heavily pre-treated patients, the 2-year progression-free survival (PFS) is only 31%.[7] Those patients who progress on ibrutinib have a very poor prognosis, with an OS of 8 months.[8] Novel approaches are required to improve outcomes for patients with relapsed/refractory MCL, and to improve the remission duration for patients completing their initial therapy.

1.2 Background/Rationale

Proteasome inhibition remains an integral approach to the management of MCL. The single agent ORR of bortezomib in the relapsed/refractory setting is 33%, including 8% complete response (CR) rate, and the median duration of response is roughly 9 months. However, among patients achieving a CR, the median time to progression is 14.6 months, suggesting that a subset of patients can have prolonged responses.[6] Bortezomib has also been studied in the post-transplant maintenance setting, where the 5-year PFS for patients treated on CALGB 50403 was 73%, compared to 52% for patients treated on the prior trial (CALGB 59909) where bortezomib was omitted (p=0.0006).[3,9] Bortezomib has also been evaluated in the front-line setting and as part of the conditioning regimen for patients undergoing ASCT.[10,11] Despite the activity in MCL, bortezomib is associated with toxicities, most notably peripheral neuropathy, which occurred at grade 3 or higher in 13% of patients enrolled on the single agent study.[6]

While bortezomib and proteasome inhibition represents an effective therapy for a subset of patients, the novel Bruton's tyrosine kinase (BTK) inhibitor, ibrutinib has an even higher ORR of 68% and appears to be well-tolerated.[4] Ibrutinib is not curative and better outcomes are possible through novel drug combinations. Through combinational drug screening in pre-clinical models, promising agents with synergistic cytotoxicity have been identified. In a collaborative effort between the University of Virginia and MD Anderson, we have evaluated drugs with targets close to BTK in the B-Cell Receptor (BCR) pathway (proximal) as well as drugs with targets far from BTK or not clearly in the BCR pathway (distal) (Figure 2).[12]

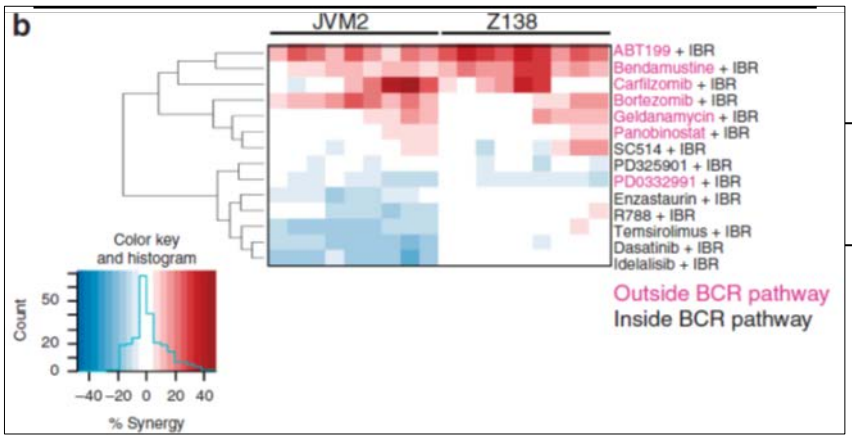
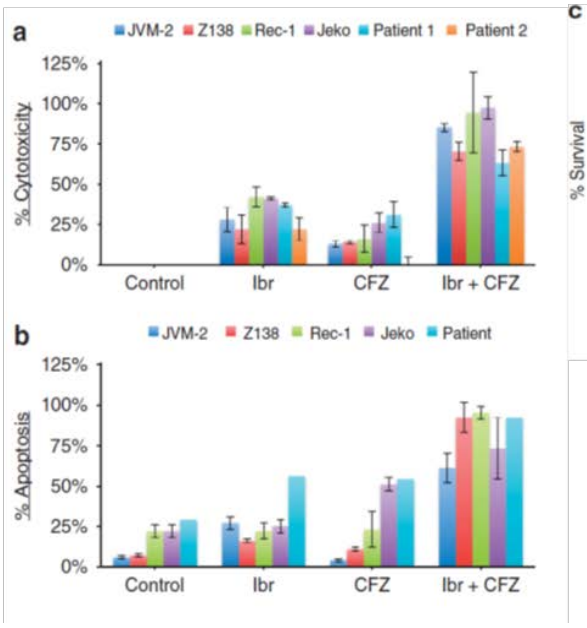


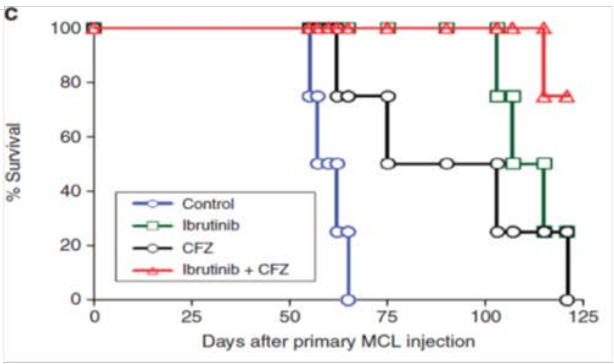
Figure 2. Hierarchical clustering of % synergy by cytotoxicity.

The initial drug screen identified drugs distal to BTK, specifically ABT-199 and proteasome inhibitors, as promising agents with synergistic cytotoxicity and apoptosis with ibrutinib. In pre-clinical models, there is significant synergy between proteasome inhibitors and ibrutinib in both direct cytotoxicity (Figure 3a) and apoptosis induction (Figure 3b). Proteasome inhibitor and ibrutinib combination also had an improved survival in a mouse-human xenograft model (Figure 4).[12]

Figure 3. % cytotoxicity of ibrutinib and carfilzomib in MCL cell lines and patient samples.

Figure 4. OS in xenograft model.





The orally available proteasome inhibitor, ixazomib, is currently under investigation in lymphoma and multiple myeloma. Ixazomib citrate (MLN9708) is immediately converted to its active metabolite, Ixazomib (MLN2238), upon ingestion, resulting in inhibition of TNFα-induced activation of NFκB. In WSU-DLCL2 tumor-bearing mice, MLN2238 generated a stronger anti-tumor activity and greater apoptotic response (measured by levels of cleaved caspase-3) compared to bortezomib. In a murine disseminated lymphoma model (NOD-SCID mice inoculated with OCI-Ly7-Luc cells) anti-tumor activity of MLN2238 was better

than bortezomib, where median OS was 54 days for mice exposed to MLN2238 compared to 33 days for vehicle controls (p=0.05). Median OS was not significantly different for bortezomib-treated mice compared to those exposed to vehicle controls (p>0.99).[13] In a subsequent experiment evaluating in vivo activity of ixazomib in OCI-Ly10 tumor-bearing SCID mice, the anti-tumor activity (treated vs. control; T/C) of ixazomib was improved (T/C = 0.37) compared to bortezomib (T/C = 0.68) in this model based on a human cell line of activated-B-cell like diffuse large B-cell lymphoma. In vivo anti-tumor activity was also demonstrated in PHTX22L tumor-bearing NOD-SCID mice (T/C for ixazomib 0.14, p<0.01), while bortezomib did not demonstrate significant anti-tumor activity.[14]

Based on these pre-clinical findings in murine models, ixazomib has been evaluated in early phase clinical trials. In a phase I study of the IV formulation of ixazomib in relapsed/refractory Non-Hodgkin's Lymphoma (NHL), 30 patients were treated at 8 dose levels, including 10 at the maximum tolerated dose (MTD) of 2.34 mg/m^2 on days 1, 8, and 15. Five of twenty-six patients responded, with durations ranging from 6-33 months. Ten percent of patients discontinued due to an adverse event, and the most common adverse events were neutropenia, gastrointestinal (GI) toxicity, and acute renal failure secondary to GI toxicity.[15] Ixazomib has also been evaluated alone and combined with other agents in multiple myeloma, where the oral formulation has a MTD of 2.97 mg/m^2 on days 1, 8, and 15 of 28 day cycles. Notably, there were no instances of grade 3-4 peripheral neuropathy in a single agent phase I study of weekly ixazomib.[16] An additional phase I study of twice-weekly ixazomib in multiple myeloma found an MTD of 2.0 mg/m^2 on days 1, 4, 8, and 11 of a 21 day cycle, with only 11% of patients experiencing peripheral neuropathy and no cases of grade 3-4 neuropathy.[17] Ixazomib is also being investigated in combination with dexamethasone and lenalidomide in relapsed myeloma.[18] It continues to be investigated in ongoing studies alone and in combination in both lymphoma and multiple myeloma, including one study combining ixazomib with lenalidomide for post-transplant maintenance in multiple myeloma (NCT01718743) and combination studies are planned in lymphoma.

1.3 Ixazomib (MLN9708)

1.3.1 Preclinical Experience

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

1.3.2 Clinical Experience

Ixazomib has been evaluated as an oral single agent in phase 1, phase 1/2 and phase 2 studies in multiple myeloma (MM), systemic light-chain amyloidosis (AL), solid tumors, and lymphoma. In addition, Phase I studies are completed in patients with renal or hepatic impairment to evaluate the effect on food on ixazomib pharmacokinetics (PK), to evaluate drug-drug interactions (DDI's), and to characterize ixazomib absorption, distribution, metabolism, and excretion (ADME) have been conducted. Phase 3 trials in RRMM, newly diagnosed multiple myeloma (NDMM), and relapsed or refractory systemic light-chain amyloidosis (RRAL amyloidosis) are underway. As of 27 March 2017, data are available from 941 patients who have received at least 1 dose of either the IV or oral ixazomib formulations across the clinical development program; in addition, 2682 patients have enrolled in 7 phase 3 clinical trials:

- Double-blind, placebo-controlled Global Study C16010 and Study C16010 China continuation study (CCS) of ixazomib versus placebo in combination with LenDex in patients with RRMM
- Double-blind, placebo-controlled Study C16014 and Study C16014 South Korea extension study (KES) of ixazomib versus placebo in combination with LenDex in patients with NDMM

- Double-blind, placebo-controlled Study C16019 of ixazomib versus placebo as maintenance in patients with NDMM
- Open-label Study C16011 of ixazomib and dexamethasone versus physician's choice of a dexamethasone-containing regimen in patients with AL amyloidosis

Regardless, of the route of administration, in the twice-weekly dosing schedule ixazomib is given on Days 1, 4, 8, and 11 of a 21-day cycle, and in the weekly dosing schedule ixazomib is given on Days 1, 8, and 15 of a 28-day cycle (approved schedule).

In 2015, FDA approval was received for ixazomib (NINLARO®) in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.

Adverse events (AEs) observed to date (as of 27 March 2017) are generally reversible, are manageable with standard medical interventions, and are dose dependent. The type of AEs are generally consistent across the patient populations treated to date, though some AEs may be more common either due to the patient population or the regimen being studied (e.g., thrombocytopenia is more common with weekly single-agent ixazomib in RRMM than in RRAL amyloidosis; thrombocytopenia is more common with weekly ixazomib + LenDex in RRMM than ixazomib + LenDex in NDMM; myelosuppression is more common overall when ixazomib is combined with MelPred; nausea is common across studies; and diarrhea is more common with weekly ixazomib + LenDex than with single-agent ixazomib). Such differences may illustrate effects of the disease or prior therapy on the body (e.g., on the bone marrow) as well as the side effect profile of the agents in a combination regimen.

The most commonly observed ($\geq$ 30% incidence) treatment-emergent AEs (TEAEs) from pooled data across clinical studies with oral ixazomib include nausea and diarrhea (43% each), fatigue (39%), rash (all terms; 36%), and vomiting (33%). The frequency of rash is noted in an aggregate because it is characterized in different ways; however, it is less common when considering individual preferred terms.

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

1.3.3 Pharmacokinetics and Drug Metabolism

After oral dosing, absorption of ixazomib is rapid with a median first time to maximum observed plasma concentration (T_{max}) of approximately 1 hour post dose. The plasma exposure (AUC) of ixazomib increases in a dose-proportional manner over a dose range of 0.2 to 10.6 mg based on population PK analysis.[19] The absolute oral bioavailability (F) of ixazomib is estimated to be 58% based on population PK analysis. A high-fat meal reduced ixazomib C_{max} by 69% and AUC_{0-216} by 28%. This indicates that a high-fat meal decreases both the rate and extent of absorption of ixazomib. Therefore, ixazomib should be taken on an empty stomach (at least 2 hours after food or 1 hour before food).

Detailed information regarding pharmacokinetics and drug metabolism is available in the IB.

1.3.4 Clinical Trial Experience Using the Oral Formulation of Ixazomib

As of the clinical data cutoff of 27 March 2017, there are 16 ongoing oncology clinical studies of ixazomib, and 9 completed studies.

These patients have been treated with different doses of ixazomib either as a single-agent treatment or in combination with currently clinically available treatments.

Information regarding the ongoing studies, patient populations, and doses investigated is included in the IB.

Ixazomib is currently FDA-approved for the treatment of relapsed multiple myeloma in combination with lenalidomide and dexamethasone. The FDA-approved dose is 4 mg on days 1, 8, and 15 of a 28-day cycle.

1.3.5 Overview of the Oral Formulation of Ixazomib

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

In the 4 ongoing studies (C16003, C16004, C16007, and C16009) investigating single-agent oral ixazomib in patients with differing malignancies (multiple myeloma, AL amyloidosis, non-hematologic cancers, and lymphoma), a total of 259 patients have been treated as of 27 March 2017. These patients have been treated with different doses of ixazomib as they are all phase 1 trials. An overview of the most frequent (at least 10%) AEs occurring in the pooled safety population from single-agent oral ixazomib Studies (C16003, C16004, C16007, and C16009) is provided in the latest IB.

The clinical experience with ixazomib also shows early signs of antitumor activity as evidenced by at least a 50% reduction in disease burden in some patients and prolonged disease stabilization in others across all ongoing trials. The antitumor activity has been seen with single-agent ixazomib, when combined with established therapies, and across the malignancies studied (advanced solid tumors[20], non-Hodgkin's disease, Hodgkin's disease[21], RRMM[22,23], relapsed or refractory systemic light chain amyloidosis [RRAL][24], and NDMM[25,26,27]) to date.

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

1.3.6 Clinical Trial Experience with Ixazomib in NHL[28]

Ixazomib was evaluated in IV form in a dose-escalation study for nearly all lymphoma subtypes. Patients received an IV bolus on days 1, 8, and 15 of a 28-day cycle for up to 12 months. Thirty patients received therapy, including 2 patients with MCL. The majority of patients had follicular lymphoma (n=11), diffuse large b-cell lymphoma (n=5) and peripheral T-cell lymphoma (n=4). Four DLT's were identified, including neutropenia (n=2), acute renal failure (n=1) and one patient with fatigue, nausea, vomiting, and diarrhea. Ultimately, 2.34 mg/m^2 was determined to be the MTD using the IV formulation. Additional grade ≥3 drug-related toxicities included neutropenia (n=6), thrombocytopenia (n=4), diarrhea (n=3), and dehydration, lymphopenia, renal failure, and skin disorders (n=2).

Five of 26 evaluable patients experienced a complete or partial response, including 3 with follicular lymphoma and 1 patient with peripheral T-cell lymphoma. Six additional patients (including a MCL patient) had stable disease lasting a median of 3.6 months.

A study of oral ixazomib in relapsed/refractory follicular lymphoma has recently been completed (NCT01939899).

1.4 Ibrutinib

The Bruton's tyrosine kinase inhibitor (BTK) ibrutinib (Imbruvica®) was FDA approved for the management of previously treated MCL in 2013 based on the results of a single agent phase II study. The FDA-approved dose for MCL is 560 mg once daily. In the pivotal phase II study, which incorporated bortezomib-pretreated and -naïve patients, the ORR was 67%, a significant improvement over previously reported single-agent response rates for bortezomib and lenalidomide.[4-6] In addition to this response rate, the median duration of response is 17.5 months. Additional therapy options, including combination therapy and novel treatments are currently under investigation. In addition to single agent studies, ibrutinib has been evaluated in combination in MCL. In a phase Ib/II study of ibrutinib, rituximab, and bendamustine, the ORR for the patients with MCL (n=17) was 94%.[29] When combined with rituximab alone in relapsed/refractory MCL, the ORR (n=45) is 87%, while 100% of patients with a Ki67 <50% responded.[30]

Despite the promising results with single agent ibrutinib, resistance mechanisms are emerging, including most notably, the C481S mutation of BTK.[31] In a recent update of long-term follow-up for the phase II study, the 2-year PFS was only 31%, indicating that a substantial portion of treated patients will progress within the first 2 years.[7] Patients who progress on ibrutinib have demonstrated aggressive disease behavior and shortened overall survival.[8]

1.4.1 Toxicity[32]

Ibrutinib-related toxicity continues to be better understood with prolonged follow-up. While most patients tolerate prolonged therapy, several associated toxicities have emerged, which are described below based on the package insert. While many are manageable, these toxicities must be monitored and addressed for all patients who are receiving prolonged therapy.

1.4.1.1 Hemorrhage

Fatal bleeding events have occurred in patients treated with ibrutinib. Grade 3 or higher bleeding events (subdural hematoma, gastrointestinal bleeding, hematuria and post procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with ibrutinib. The mechanism for the bleeding events is not well understood. Ibrutinib may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies. Consider the benefit-risk of withholding ibrutinib for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding.

1.4.1.2 Infections

Fatal and non-fatal infections have occurred with ibrutinib therapy. Grade 3 or greater infections occurred in 14% to 26% of patients. Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with ibrutinib. Monitor patients for fever and infections and evaluate promptly.

1.4.1.3 Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 19 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 9%) occurred in patients treated with ibrutinib.

1.4.1.4 Atrial Fibrillation

Atrial fibrillation and atrial flutter (range, 6 to 9%) have occurred in patients treated with ibrutinib, particularly in patients with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness) or new onset dyspnea should have an ECG performed. If atrial fibrillation persists, consider the risks and benefits of ibrutinib treatment and dose modification.

1.4.1.5 Second Primary Malignancies

Other malignancies (range, 5 to 14%) including non-skin carcinomas (range, 1 to 3%) have occurred in patients treated with ibrutinib. The most frequent second primary malignancy was non-melanoma skin cancer (range, 4 to 11 %).

1.4.1.6 Tumor Lysis Syndrome

Tumor lysis syndrome has been reported with ibrutinib therapy. Monitor patients closely and take appropriate precautions in patients at risk for tumor lysis syndrome (e.g. high tumor burden).

In the recently published long-term follow-up for patients with MCL treated with single agent ibrutinib, the following recurrent serious adverse events were reported:

Table 1-1 Ibrutinib: Recurrent Serious Adverse Events

	Total (N=111)		
SAE*, n (%)	**Any Grade**	**Grade 3-4**	**Grade 5**
Disease Progression	11 (10%)	3 (3%)	8 (7%)
Pneumonia	8 (7%)	7 (6%)	1 (1%)
Atrial Fibrillation	7 (6%)	6 (5%)	0
Urinary Tract Infection	4 (4%)	3 (3%)	0
Febrile Neutropenia	3 (3%)	3 (3%)	0
Abdominal Pain	3 (3%)	3 (3%)	0
Acute Renal Failure	3 (3%)	2 (2%)	1 (1%)
Subdural hematoma	3 (3%)	2 (2%)	0
Pyrexia	3 (3%)	1 (1%)	0
Confusional State	3 (3%)	1 (1%)	0

1.5 Summary of Rationale for Proposed Study

1.5.1 Rationale

Single agent therapy for patients with relapsed MCL can result in responses that are durable for some patients but is not curative. With continued follow-up, it is evident that most patients will relapse within 2 years. As a result, we plan to build upon the successes of recently identified novel therapies by investigating a novel, all oral combination of ixazomib and ibrutinib. These agents appear to have synergy in pre-clinical assessments, as ibrutinib appears to result in increased cell death for MCL cells that are previously bortezomib-resistant when they are exposed to the combination.[33]

While bortezomib is effective as a single agent in several settings in MCL, it is associated with dose-limiting peripheral neuropathy and also requires serial injections. Ixazomib is available orally and appears to have decreased peripheral

neuropathy, allowing for an all oral therapy for patients with relapsed MCL. As a result, we will proceed with a phase I/II study of ixazomib and ibrutinib in combination for relapsed/refractory mantle cell lymphoma. The phase I portion of the study will be designed to identify the appropriate dose of ixazomib when combined with ibrutinib in this setting, and the phase II portion of the study will assess the efficacy of this combination.

1.5.2 Rationale for the Study Design and Treatment Plan

We have elected to enroll both BTK-pretreated and BTK-naïve patients for this study. For the phase I portion of the study, which is focused primarily on safety and tolerability, all patients will be enrolled regardless of prior ibrutinib exposure. However, we will require ibrutinib pre-treated patients to satisfy specific criteria (Eligibility Criteria 3.4) in order to avoid rapid progression during the first cycle of therapy which would make dose limiting toxicity assessment challenging.

Phase I Summary: Three patients were enrolled to Dose Level 1 with no DLTs during the 28 day assessment period. Nine patients were enrolled to Dose Level 2, five of the nine patients completed the 28 day assessment period with no DLTs. One patient experienced a grade 3 lung infection that was considered a DLT. Three of the nine patients were not evaluable for DLT and were replaced. One patient was inadvertently given neulasta prior to receiving Cycle 2, Day 1 therapy; another patient unintentionally took Day 15 ixazomib on Day 9; and one patient forgot to take ibrutinib the last 8 days of Cycle 1 unrelated to any toxicities. The Phase I portion of the study was completed November 25, 2019. Dose Level 2 is the recommended Phase 2 dose with ixazomib 4 mg on Days 1, 8 and 15 of a 28 day cycle and ibrutinib 560 mg on Days 1-28 of a 28 day cycle.

For the phase II portion of the study, we have developed two dosing cohorts (BTK-pretreated and BTK-naïve), so that we can assess the efficacy of this combination in both settings. Based on the preclinical evidence of synergy, it is our hope and expectation that patients who have previously progressed on single agent ibrutinib or other BTK inhibitor will still achieve benefit when they receive the combination. Efficacy will be assessed separately for each cohort, with success determined based on historical cohorts. For BTK-pretreated patients, we will use the previously reported CR rate for bortezomib, while for BTK-naïve patients we will compare our results to the previously reported single agent activity of ibrutinib, using CR rate as the primary endpoint.

August 7, 2020: Phase II opened December 17, 2019 with Cohort A: BTK-naïve or Cohort B: BTK-pretreated.

Enrollment to Cohort A: BTK-naïve will continue. We plan to reach our original accrual goal of 36 BTK-naïve subjects treated at the established Dose Level 2 for 31 eligible, treated patients. The Phase I BTK-naïve patients treated at Dose Level 2 will be included in the 36 patient total. Seventeen additional BTK-naïve patients will be enrolled to complete this cohort.

Enrollment to Cohort B: BTK-pretreated will close. To date, only two patients have enrolled in Cohort B.

2. Study Objectives

2.1 Primary Objective

2.1.1 Phase I

To determine the maximum tolerated dose (MTD) of ixazomib in combination with ibrutinib in patients with relapsed/refractory mantle cell lymphoma (MCL).

2.1.2 Phase II

To determine the complete response (CR) rate of ixazomib in combination with ibrutinib in relapsed/refractory MCL in BTK-naïve patients.

2.2 Secondary Objectives

2.2.1 Phase I

- To evaluate regimen-related toxicities for the combination of ixazomib and ibrutinib in relapsed/refractory MCL.
- To evaluate preliminary evidence of efficacy by describing the overall response rate (ORR) for the combination.
- To evaluate evidence of efficacy by describing the median progression-free (PFS) and overall survival (OS) for patients treated with this combination.

2.2.2 Phase II

- To evaluate the ORR of the combination of ixazomib and ibrutinib.
- To evaluate PFS and OS for patients treated with the combination.
- To further evaluate regimen-related toxicity for patients treated with ixazomib and ibrutinib.

2.3 Exploratory Objectives

- [redacted]
- [redacted]
- [redacted]
- [redacted]

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

PrECOG Patient No. _____

Patient's Initials (F, M, L) _____

Physician Signature and Date _____

NOTE: PrECOG does not allow waivers to any protocol specified criteria. All eligibility criteria listed in Section 3 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 3 can result in the participant being censored from the analysis of the study, and a major protocol violation. All questions regarding clarification of eligibility criteria must be directed to the Medical Monitor or PrECOG Study Contact.

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration by the treating physician.

_____ 3.1 Patients must have relapsed or refractory, pathologically proven mantle cell lymphoma. Patients must have a current or prior tissue sample that is IHC positive for cyclin D 1 or that is positive by FISH or cytogenetics for t(11;14).

Date of Relapse/Refractory MCL: _____

_____ 3.2 Patients must have been refractory to and/or relapsed/progressed after at least 1 prior therapy.

Date of Last Therapy: _____

_____ 3.3 Prior autologous or allogeneic transplant are allowed. Patients may not have active grade II-IV acute GVHD or moderate/severe chronic GVHD by NIH criteria and may not require immunosuppressive medications and/or corticosteroids for the management of acute or chronic GVHD.

_____ 3.4 **Phase I:** Prior proteasome inhibitor and/or Bruton's tyrosine kinase inhibitors are allowed but patients may not have been exposed to the combination of proteasome inhibitor and BTK inhibitor. Patients who have progressed on ibrutinib that are felt to be at high risk for rapid progression on this study shall not be eligible for the phase I portion of the study. **NOTE: Ibrutinib pre-treated patients must meet all eligibility criteria AND must have discontinued prior ibrutinib at least 3 months prior to starting study therapy.**

Pretreated with ibrutinib: ☐ Yes ☐ No

If yes, does patient meet criteria above: ☐ Yes ☐ No

PHASE I COMPLETED NOVEMBER 25, 2019.

Phase II: Prior proteasome inhibitors allowed.

(Please note prior to Version 3.0 of the protocol prior proteasome inhibitor and/or Bruton's tyrosine kinase inhibitors were allowed but patients could not have been exposed to the combination of proteasome inhibitor and BTK inhibitor).

_____ 3.5 Age ≥ 18 years.

_____ 3.6 ECOG performance status of 0-2 (Appendix I).

_____ 3.7 Ability to understand and willingness to sign IRB-approved informed consent.

_____ 3.8 Willing to provide archived tumor tissue, bone marrow (if sufficient bone marrow and tumor tissue are available) and blood samples for research (Section 13.0).

_____ 3.9 Adequate organ function as measured by the following criteria, obtained ≤ 2 weeks prior to registration:

- Absolute Neutrophil Count (ANC) ≥ 750/mm^3

  ANC: _____ Date of Test: _____

- Platelets >50,000/mm^3

  Platelets: _____ Date of Test: _____

  NOTE: Platelet transfusions are not allowed within 3 days before registration to meet eligibility criteria.

- Serum Creatinine ≤ 2x Upper Limit Normal (ULN)

  Serum Creatinine: _____ ULN: _____ Date of Test: _____

- ALT and AST ≤ 3x ULN

  ALT: _____ Institution ULN: _____ Date of Test: _____

  AST: _____ Institution ULN: _____ Date of Test: _____

- Total Bilirubin ≤ 1.5x ULN (in the absence of previously diagnosed Gilbert's disease)

  Total Bilirubin: _____ ULN: _____ Date of Test: _____

_____ 3.10 Patients must not have received systemic treatment for MCL for at least 14 days prior to enrollment, except for steroids which may be used to manage acute symptoms related to disease up to 48 hours prior to starting study therapy. Radiation therapy must be concluded at least 14 days prior to enrollment.

_____ 3.11 Women must not be pregnant or breastfeeding since we do not know the effects of ixazomib and ibrutinib on the fetus or breastfeeding child. All sexually active females of childbearing potential (not surgically sterilized and between menarche and 1 year post menopause) must have a blood test to rule out pregnancy within 2 weeks prior to registration.

Is the patient a woman of childbearing potential? _____ (yes/no)

If yes, Date of Test: _____ Results: _____

_____ 3.12 Sexually active women of child-bearing potential with a non-sterilized male partner and sexually active men must agree to use 2 methods of adequate contraception (hormonal plus barrier or 2 barrier forms) OR abstinence prior to study entry, for the duration of study participation, and for 3 months following last dose of study drugs.

NOTE: Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

_____3.13 Patients must have resolved all prior non-hematologic toxicities assessed as related to prior therapy to ≤ grade 1.

_____3.14 Patients must have measurable disease (i.e., ≥ 1.5 cm in largest diameter) by conventional imaging modalities. Patients with extranodal involvement as the only measurable site of disease must have a largest diameter greater than ≥ 1.0 cm and must be attributable to active lymphoma in the opinion of the investigator.

_____ 3.15 Patients may not have current/active Central Nervous System (CNS) involvement with mantle cell lymphoma (patients with prior CNS involvement are eligible as long as they have had no evidence of active CNS disease for at least 6 months). Patients without clinical evidence of CNS involvement do not require CNS assessment at screening.

_____ 3.16 Patients may not have another malignancy that could interfere with the evaluation of safety or efficacy of this combination. Patients with a prior malignancy will be allowed without study chair approval in the following circumstances:

1) Not currently active and diagnosed at least 3 years prior to the date of enrollment.
2) Non-invasive diseases such as low risk cervical cancer or any cancer in situ.
3) Localized disease in which chemotherapy would not be indicated (such as Stage I colon, lung, prostate or breast cancer). Patients with other malignancies not meeting these criteria must be discussed with PrECOG prior to enrollment.

_____ 3.17 Patients requiring long-term anticoagulation must be managed on an anticoagulant besides warfarin. Patients who require warfarin are not eligible.

_____ 3.18 Patients with a clinically significant bleeding episode as judged by the investigator within 3 months of registration are not eligible, except patients who suffer bleeding due to trauma.

_____ 3.19 Patients may not have had major surgery within 14 days, or minor surgery within 3 days, before registration.

_____ 3.20 Patients may not have any active infection requiring oral or intravenous antimicrobial therapy at the time of therapy initiation. Patients with a recent self-limited infection that has clinically resolved may complete a prescribed course of antimicrobial therapy after study initiation as long as they are asymptomatic with no clinical evidence of infection for at least 7 days prior to treatment. Patients with a recent serious (grade ≥ 3) infection requiring hospitalization must have completed all antimicrobial therapy within 14 days of therapy initiation.

_____ 3.21 Patients may not have evidence of uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, symptomatic congestive heart failure (NYHA class III or higher [Appendix II]), unstable angina, or myocardial infarction within the past 6 months. Patients with a history of any significant cardiovascular disease that has been controlled for at least 14 days before registration are allowed (except for patients who have had a myocardial infarction within 6 months).

_____ 3.22 No systemic treatment, within 14 days before the first dose of ibrutinib with moderate or strong inhibitors of CYP3A (Strong Inhibitors: ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, and telithromycin; Moderate Inhibitors: fluconazole, darunavir, erythromycin, diltiazem, atazanavir, aprepitant, amprenavir, fosamprenavir, crizotinib, imatinib, verapamil, ciprofloxacin, grapefruit juice products, and Seville oranges) or strong CYP3A inducers for ibrutinib and ixazomib (carbamazepine, rifampin, phenytoin, St. John's wort). Refer to Section 11.2.7 for additional excluded medications and information.

_____ 3.23 Patients with ongoing or active systemic infection, active hepatitis B or C virus infection, or known Human Immunodeficiency Virus (HIV) positive are not eligible. Testing is not required in absence of clinical suspicion.

_____ 3.24 Patients with a history of hepatitis B or C must have a negative peripheral blood Polymerase Chain Reaction (PCR) and may not be positive for Hepatitis B surface antigen. Patients with cirrhosis or other evidence of liver damage due to Hepatitis B or C are not eligible.

_____ 3.25 Patients with any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of the treatment according to the protocol are not eligible.

_____ 3.26 Patients with a known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent are not eligible.

_____ 3.27 Patients with known GI disease or prior GI procedure that could interfere with the oral absorption or tolerance of ixazomib or ibrutinib including difficulty swallowing are not eligible.

_____ 3.28 Patients with ≥ Grade 2 peripheral neuropathy, or Grade 1 peripheral neuropathy with pain on clinical examination during the screening period are not eligible.

_____ 3.29 Patients may not participate in any other therapeutic clinical trials, including those with other investigational agents not included in this trial throughout the duration of this study.

_____ 3.30 As ibrutinib will not be provided by the study, the patient must be able to obtain ibrutinib through other means (i.e., commercially or through patient assistance programs). This must be confirmed prior to registration.

4. Registration Procedures

4.1 Ethics

This study will be conducted in accordance with the ethical principles that have their origin in the current Declaration of Helsinki and will be consistent with applicable US regulatory requirements and International Conference on Harmonization/Good Clinical Practice (ICH/GCP).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the patient informed consent will receive Institutional Review Board (IRB) approval prior to initiation of the study.

Freely given written informed consent must be obtained from every patient or their legally acceptable representative prior to clinical trial participation, including informed consent for any screening procedures conducted to establish patient eligibility for the trial.

Study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s). This trial will not use the services of investigators or study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment). Investigators are responsible for the conduct of the study at their study site.

4.2 Regulatory Requirements

Before a site may enter patients, protocol-specific regulatory and other documents must be submitted to PrECOG as noted in study materials. Detailed information regarding document submission and control is provided to each site in separate study materials.

Once required documents are received, reviewed, and approved by PrECOG or their representative, a Study Reference Manual (SRM) will be forwarded to the site. Any changes to site regulatory documents must be submitted by the investigator to the responsible party in a timely manner. Initial study drug shipment will not occur until the regulatory packet is complete. No patients will begin protocol therapy without formal registration as per the process below.

4.3 Phase I and II Patient Registration

Patients must meet all of the eligibility requirements listed in Section 3 prior to registration. Treatment should begin ≤ 10 working days from study entry (date of registration).

An eligibility checklist is included in Section 3. A confirmation of eligibility assessment by the investigator and/or site will be performed during the registration process.

Phase I Registration – Prior to discussing protocol entry with the patient **AND** prior to registering in the electronic data capture (eDC) system, call the assigned PrECOG Project Manager to ensure that a place on the protocol is open to the patient. An Enrollment Approval Form must be completed prior to registration.

Upon determination that a subject meets eligibility criteria, the subject will be registered in the study by site personnel via an electronic data capture (eDC) system. Confirmation of registration will be displayed in the eDC system. Detailed registration procedures and study contacts will be outlined in the SRM.

The phase II portion will be conducted using the dose and schedule selected from the phase I portion of the study. Before proceeding to phase II, the protocol will be amended to specify the final dose selected from phase I. Patients that participate in phase I will not be eligible to participate in phase II.

Phase II Registration – After it is verified by the site that the patient meets all eligibility criteria, registration will occur by entering the patient in the eDC system.

Full information regarding registration procedures and guidelines can be found in the SRM provided to your site. Correspondence regarding patient registration must be kept in the study records.

Patients must not start protocol treatment prior to registration.

4.4 Research Bone Marrow, Tissue and Blood Samples

Mandatory bone marrow and tumor tissue samples are required at baseline (if sufficient bone marrow and tumor tissue are available, submission is mandatory).

Mandatory peripheral blood samples will also be collected.

NOTE: No bone marrow biopsy/aspirate or tissue biopsy should be performed solely for the purposes of obtaining research samples.

Time points for bone marrow, tissue and blood samples are outlined in the study parameters (Section 10) and specific requirements are outlined in the correlative section of this protocol (Section 13) and the lab manual.

5. Study Design

5.1 Phase I

The phase I portion of the study will accrue patients in a standard 3+3 design with the primary objective of determining the maximum tolerate dose (MTD)/recommended phase 2 dose (RP2D) of this combination in MCL. Both ibrutinib-pretreated and ibrutinib-naïve patients will be enrolled. Planned dose levels are described below. There will be no dose escalation above Dose Level 2. If dose level 1 is too toxic, we will de-escalate to dose level (-1). There shall be no dose reductions below dose level (-1).

Open to Ibrutinib Naïve and Selected Pretreated Patients →

Dose Level	Ixazomib Days 1, 8, 15 of a 28 Day Cycle	Ibrutinib Days 1-28 of a 28 Day Cycle
-1	3 mg	420 mg
1 **Starting Dose**	3 mg	560 mg
2	4 mg	560 mg

NOTE: For the phase I portion of the study, ibrutinib pre-treated patients must meet all eligibility criteria AND must have discontinued prior ibrutinib at least 3 months prior to starting study therapy.

Three patients were enrolled to Dose Level 1 with no DLTs during the 28 day assessment period. Nine patients were enrolled to Dose Level 2. Five of the nine patients completed the 28 day assessment period with no DLTs, and one patient experienced a Grade 3 lung infection that was considered a DLT. Three of the nine patients were not evaluable for DLT and were replaced. One patient was inadvertently given neulasta prior to receiving Cycle 2, Day 1 therapy; another patient unintentionally took Day 15 ixazomib on Day 9; and one patient forgot to take ibrutinib the last 8 days of Cycle 1 unrelated to any toxicities. **Phase I was completed November 25, 2019. Dose Level 2 is the recommended Phase 2 dose.**

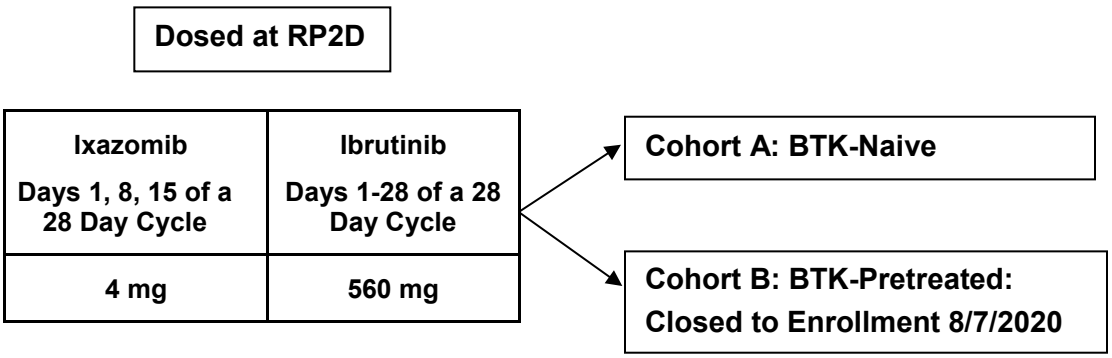
5.2 Phase II

Once dose escalation and de-escalation has completed with determination of the MTD/RP2D **(Phase I completed November 25, 2019)**, the phase II portion of the study will begin. Patients will be enrolled to two cohorts, based on prior BTK inhibitor treatment: BTK-pretreated and BTK-naïve **(see below)**. Patients will be treated until disease progression or until unacceptable toxicity, with dose modifications and delays as described in Section 6.5.

August 7, 2020: Phase II opened December 17, 2019 with Cohort A: BTK-naïve or Cohort B: BTK-pretreated.

Enrollment to Cohort A: BTK-naïve will continue. We plan to reach our original accrual goal of 36 BTK-naïve subjects treated at the established Dose Level 2 for 31 eligible, treated patients. The Phase I BTK-naïve patients treated at Dose Level 2 will be included in the 36 patient total. Seventeen additional BTK-naïve patients will be enrolled to complete this cohort.

Enrollment to Cohort B: BTK-pretreated will close. To date, only two patients have enrolled in Cohort B.


Dosed at RP2D
Ixazomib
Days 1, 8, 15 of a 28 Day Cycle
Ibrutinib
Days 1-28 of a 28 Day Cycle
4 mg
560 mg
Cohort A: BTK-Naive
Cohort B: BTK-Pretreated:
Closed to Enrollment 8/7/2020

6. Treatment Plan

6.1 Overview

This study shall be divided into phase I and phase II components. The phase I portion of the study shall be designed to evaluate the safety and tolerability of the combination of ibrutinib and ixazomib in relapsed/refractory MCL and to identify the MTD/RP2D. The phase II portion of the study will evaluate the efficacy of this combination.

6.1.1 Ixazomib Administration

Ixazomib will be administered orally. Patients should be instructed to swallow ixazomib capsules whole, with water, and not to break, chew, or open the capsules. Ixazomib should be taken on an empty stomach (no food or drink) at least 1 hour before or at least 2 hours after food. Each capsule should be swallowed separately with a sip of water. A total of approximately 8 ounces (240 mL) of water should be taken with the capsules. A Medication Diary will be provided to the patient to record each date and dose of ixazomib after Cycle 1 (Appendix III).

Missed doses can be taken as soon as the patient remembers if the next scheduled dose is ≥ 72 hours for all cycles aside from Cycle 1 of the phase 1 study. Patients with dose delays in Phase I, Cycle 1 shall be managed as described below in Section 6.2 and Section 6.2.1. A double dose should not be taken to make up for a missed dose. If the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose.

Patients on Cycle 2 and beyond of the phase I study and those enrolled on the phase II study shall not make up any ixazomib doses that are delayed >72 hours due to toxicity.

6.1.2 Ibrutinib Administration

Ibrutinib will be administered orally. Doses should be taken at the same time each day without regard to food or drink (except as noted in Section 6.6.2). Ibrutinib should be swallowed whole with water and the tablets should not be opened, broken, or chewed. A Medication Diary will be provided to the patient to record each date and dose of ibrutinib (Appendix IV).

If a dose of ibrutinib is not taken at the scheduled time, it can be taken as soon as possible up to 8 hours after the scheduled time on the same day with a return to the normal schedule the following day. If a patient does not take a dose within 8 hours of the scheduled time, that day's dose will be skipped. Extra capsules of ibrutinib should not be taken to make up for the missed dose. If the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose.

6.2 Phase I Treatment Administration

Patients will be enrolled to the phase I study through a standard 3 + 3 design. Eligible patients will include ibrutinib-naïve patients as well as selected ibrutinib-pretreated patients. Given the focus of the phase I study on safety/tolerability, patients who have progressed on ibrutinib that are felt to be at high risk for rapid progression on this study shall not be eligible for the phase I portion of the study (Eligibility Criteria 3.4). This exclusion of rapid progressors is designed to decrease the risk of having to replace multiple patients due to progression during the dose-limiting toxicity (DLT) assessment period.

Dose escalation shall occur according to Table 6-1. The first three patients shall be accrued to Dose Level 1 (3 mg ixazomib and 560 mg ibrutinib). Patients shall take ibrutinib continuously once daily of a 28 day cycle. Ixazomib will be administered orally on days 1, 8, and 15 of a 28 day cycle. Patients shall continue therapy until progression or unacceptable toxicity.

Table 6-1 Dose Levels for Phase I Study

Dose Level	Ixazomib Days 1, 8, 15 of a 28 Day Cycle	Ibrutinib Days 1-28 of a 28 Day Cycle
-1	3 mg	420 mg
1 **Starting Dose**	3 mg	560 mg
2	4 mg	560 mg

The MTD/RP2D shall be defined as the highest dose level where 0 or 1 out of 6 patients experiences a DLT. The first 3 patients will be accrued to Dose Level 1. If 0 of the first 3 patients enrolled experience a DLT, then the following cohort of 3 patients will be accrued to the next highest dose level. If 1 of the first 3 patients experience a DLT, then an additional 3 patients will be accrued at the current dose level. If 2 or 3 of the first 6 patients experience a DLT, then that dose level shall be considered too toxic and dosing will occur at Dose Level (-1). If 2 or 3 patients experience a DLT at Dose Level (-1), the regimen will be considered too toxic and the trial will end. If Dose Level 2 proves safe (0 or 1 DLT's out of 3 patients), then an additional 3 patients shall be accrued to Dose Level 2. If 0-1 out of 6 total patients treated at Dose Level 2 experience a DLT, then that dose level shall be considered the RP2D and the phase 1 study shall end. There shall be no dose escalation above Dose Level 2. If 2 or 3 patients in Dose Level 2 experience a DLT, then that dose level shall be considered too toxic and Dose Level 1 shall be considered the RP2D as long as 0 or 1 out of 6 patients experiences a DLT.

Patients may delay therapy (ibrutinib and/or ixazomib) up to 1 week in Phase I, Cycle 1. In this case, subsequent doses of ixazomib must be >72 hours from the prior dose. As a result, for Phase I, Cycle 1 only, patients who delay a dose due to toxicity may delay subsequent doses up to 1 week to allow for at least a 3 day period between doses of ixazomib.

Patients on Phase I, Cycle 2 and subsequent cycles shall not make up any ixazomib doses that are delayed >72 hours due to toxicity (missed doses can be taken as soon as the patient remembers if the next scheduled dose is 72 hours or more away).

For Cycle 1, patients should receive all ixazomib doses in clinic after a provider assessment. For all subsequent cycles, patients are only required to be seen in clinic on day 1 of the cycle **(NOTE:** Cycle 2 and Cycle 3, Day 15 (and Day 22, if applicable) mandatory blood counts can be done locally).

Three patients were enrolled to Dose Level 1 with no DLTs during the 28 day assessment period. Nine patients were enrolled to Dose Level 2. Five of the nine patients completed the 28 day assessment period with no DLTs, and one patient experienced a Grade 3 lung infection that was considered a DLT. Three of the nine patients were not evaluable for DLT and were replaced. One patient was inadvertently given neulasta prior to receiving Cycle 2, Day 1 therapy; another patient unintentionally took Day 15 ixazomib on Day 9; and one patient forgot to take ibrutinib the last 8 days of Cycle 1 unrelated to any toxicities. **Phase I was completed November 25, 2019. Dose Level 2 is the recommended Phase 2 dose.**

6.2.1 DLT Assessment

Patients shall be assessed for DLT through the conclusion of Cycle 1 (i.e., prior to Cycle 2, Day 1). Patients experiencing progression or who are non-adherent to the study regimen and/or assessments will be removed from study therapy and replaced for the purposes of DLT assessment. Patients who miss 5 consecutive

doses of ibrutinib for reasons unrelated to toxicity OR who experience a dose delay of ixazomib of >72 hours for reasons unrelated to toxicity will not be considered DLT's. These patients shall be replaced for the purposes of DLT assessment and determination of the MTD/RP2D but may continue study therapy at the discretion of the investigator. DLT shall be defined according to Table 6-2. Patients who experience a DLT, may continue on study therapy. DLTs shall be managed according to Section 6.5 detailing dose modifications/delays and patient can re-start therapy once they meet criteria noted in Section 6.4.

Table 6-2 Dose Limiting Toxicities for Phase I

	Any toxicity-related dose delay >7 days of ibrutinib or ixazomib or inability to complete 3 doses of ixazomib within the first cycle due to toxicity shall constitute a DLT. A delay of >7 days of the start of Cycle 2 due to toxicity shall also constitute a DLT.
Grade 3	Non-Hematologic Toxicity aside from Grade 3 diarrhea, nausea, or vomiting which resolve within 48 hours of supportive care.
Grade 3	Thrombocytopenia with significant bleeding (defined as acute bleeding requiring a transfusion and/or hospitalization).
Grade 4	Thrombocytopenia
Grade 4	Febrile Neutropenia lasting longer than 7 days. To meet criteria for DLT, patients must remain febrile and neutropenic for >7 days. If a patient remains neutropenic but the fever resolves within 7 days, it shall not constitute a DLT.
Grade 4	Non-Hematologic Toxicity
Grade 5	Any Toxicity

6.3 Phase II Treatment Administration

Once the MTD/RP2D is determined, the phase I portion of the study shall end and the phase II portion shall begin **(Phase I completed November 25, 2019)**. For the phase II portion of the study, patients will be divided into two cohorts: BTK-pretreated and BTK-naïve. All patients who have received one dose of ibrutinib or any BTK inhibitor or more shall be assigned to the BTK-pretreated cohort. **August 7, 2020: BTK-pretreated cohort closed.**

Patients shall receive therapy at the RP2D: Ibrutinib 560 mg and Ixazomib 4 mg, with ibrutinib administered continuously daily and ixazomib administered on days 1, 8, and 15 of a 28 day cycle. Patients shall continue therapy until they have evidence of progression or unacceptable toxicity or withdrawal of consent.

Patients shall not make up any ixazomib doses that are delayed >72 hours due to toxicity (missed doses can be taken as soon as the patient remembers if the next scheduled dose is 72 hours or more away).

For Cycle 1, patients should receive day 1 and day 15 ixazomib doses in clinic after a provider assessment. For Cycle 2-7, patients are only required to be seen in clinic on day 1 of the cycle.

If patients continue on study therapy after Cycle 6, patients are required to be seen in clinic every 12 weeks (Day 1 of every 3 cycles) starting with Cycle 7.

6.4 Criteria to Begin a New Cycle of Therapy

Prior to starting a new cycle of treatment (Cycle 2 onwards), all of the following criteria must be met:

- ANC must be ≥ 1000/mm^3 (>750/mm^3 if documented bone marrow involvement at study entry [Cycle 2 only]).
- Platelet count must be ≥ 75,000/mm^3 (>50,000/mm^3 if documented bone marrow involvement [Cycle 2 only]).

NOTE: Patients with marrow involvement at study entry may start Cycle 2 with decreased ANC/platelet counts as documented above. For all other cycles, the standard criteria to start a new cycle apply.

- All other non-hematologic toxicity (except for alopecia, fatigue, and electrolyte/glucose abnormalities that are immediately reversible and/or not felt to be clinically significant) deemed at least possibly related to study therapy must have resolved to ≤ Grade 1 or to the patient's baseline condition. Study therapy related fatigue must be resolved to ≤ Grade 2.

Patients failing to meet these criteria may be delayed for up to 3 weeks (21 days) and should be restarted at adjusted dose levels as described below. Growth factors, platelet and blood transfusions may be used per institutional practice for all cycles except Cycle 1 of the phase 1 study (unless patient experiences a DLT).

6.5 Dose Delays & Modifications

All toxicities should be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE V5.0). A copy of the CTCAE V5.0 can be downloaded from the CTEP website (http://www.ctep.cancer.gov).

A +/-3 day window is allowed for scheduled ixazomib therapy, required tests and/or visits except as otherwise noted. Delays due to holidays, weekends, bad weather or other unforeseen circumstances will be permitted.

Patients who experience a dose delay during Cycle 1 of the phase 1 study shall be managed as described above in Section 6.2 and Section 6.2.1. If a patient experiences a DLT and continues on study therapy, follow the dose delays & modifications guidelines as noted in this section. **Phase I completed November 25, 2019.**

Patients on Cycle 2 and beyond of the phase I study and those enrolled on the phase II study shall not make up any ixazomib doses that are delayed >3 days due to toxicity. Missed doses can be taken as soon as the patient remembers if the next scheduled dose is 72 hours or more away, otherwise the dose shall be considered skipped and shall not be made up.

NOTE: It is the intent of this protocol to preserve the full labeled dosing of ibrutinib whenever possible. With the exception of the specified toxicities noted in Section 6.5.2, ibrutinib should be continued at full dose and on schedule for all patients, regardless of ixazomib delays or modifications. Patients who are unable to tolerate ixazomib at any dose level due to toxicity shall be removed from study therapy, except in cases of potential overlapping toxicity in which case the dose of ibrutinib may be reduced by one dose level (Table 6-6).

6.5.1 Dose Reductions/Modifications for Ixazomib and Ibrutinib

Table 6-3 Ixazomib and Ibrutinib Dose Adjustments for Hematologic Toxicities

Criteria	Action on Ixazomib	Action on Ibrutinib
Within-Cycle Dose Modifications		
• If platelet count ≤ 30 × 10^9/L or ANC ≤ 0.50 × 10^9/L on an ixazomib dosing day (other than Day 1).	• Ixazomib dose should be withheld. • Complete blood count (CBC) with differential should be repeated at least twice weekly (with 2 days between CBC's) until ANC and/or platelet counts have exceeded the pre-specified values (Section 6.4) required to initiate a treatment cycle on at least 2 occasions. • Upon recovery, ixazomib may be reinitiated with 1 dose level reduction (Table 6-5).	• If no recovery after reduction of ixazomib to 2.3 mg, then reduce ibrutinib to 420 mg dose. • If no recovery on the 420 mg dose, then discontinue study therapy.
Dose Modifications for Subsequent Treatment Cycles		
• Delay of >2 weeks in the start of a subsequent cycle due to lack of toxicity recovery (Section 6.4). • ANC ≤ 750 × 10^9/L and/or platelet count ≤ 50 × 10^9/L (except for Cycle 1 and Cycle 2; Section 6.4). • **NOTE:** Patients requiring delay of ≤ 2 weeks before starting a cycle do not require a dose reduction unless a delay has been required on more than 1 cycle, in which case the ixazomib dose should be decreased by one level (Table 6-5).	• Hold ixazomib until resolution as per criteria in Section 6.4. • Upon recovery, reduce ixazomib 1 dose level (Table 6-5). • The maximum delay before treatment should be discontinued will be 3 weeks or at the discretion of the principal investigator.	• If no recovery after reduction of ixazomib to 2.3 mg, then reduce ibrutinib to 420 mg dose. • If no recovery on the 420 mg dose, then discontinue study therapy.

6.5.1.1 Hematologic Guidelines for Subsequent Treatment Cycles with Ixazomib

- For hematologic toxicity that occurs during a cycle but recover in time for the start of the next cycle:
  - If dose was reduced within the cycle, start the next cycle at that same dose.
  - If due to toxicity timing, i.e., after Day 15 dosing thus a dose reduction was not required at that point in the cycle, reduce ixazomib by 1 dose level at the start of that cycle if the severity of the hematologic toxicity would have otherwise mandated a dose reduction.
  - Do not reduce the dose both within a cycle and at the start of the cycle for the same most severe toxicity.

Table 6-4 Ixazomib and Ibrutinib Treatment Modification (Delays, Reductions, and Discontinuations) Due to Non-Hematologic Adverse Events

Adverse Event (Severity)	Action on Ixazomib	Action on Ibrutinib	Further Considerations
Peripheral Neuropathy			
• Grade 1 peripheral neuropathy (PN) without pain	• No action.	• NONE	Grade 1 signs and symptoms: asymptomatic; without pain or loss of function; clinical or diagnostic observations only.[34]
• Grade 2 peripheral neuropathy or Grade 1 PN with pain	• Hold ixazomib until resolution to Grade ≤ 1 without pain or baseline.	• NONE	Grade 2 signs and symptoms: Moderate symptoms; limiting instrumental activities of daily living (ADL).[34]
• New or worsening Grade 2 peripheral neuropathy with pain or Grade 3	• Hold ixazomib until resolution to Grade ≤ 1 without pain or baseline. • Reduce ixazomib to next lower dose upon recovery (Table 6-5).	• NONE	Grade 3 signs and symptoms: severe symptoms; limiting self-care ADL; assistive device indicated.[34]
• New or worsening Grade 4 peripheral neuropathy	• Discontinue ixazomib.	• NONE	
Grade 2 Non-Hematologic Toxicity that was Grade ≤ 1 at baseline.	• Day 1 of cycle: Hold ixazomib until resolution to Grade ≤ 1 or baseline (except for alopecia, fatigue and electrolyte/glucose abnormalities that are immediately reversible and/or not felt to be clinically significant). Day 8 and/or 15 of cycle: No change.	• NONE	Study therapy related to fatigue must be resolved to ≤ Grade 2 to continue treatment.

Table 6-4 Ixazomib and Ibrutinib Treatment Modification (Delays, Reductions, and Discontinuations) Due to Non-Hematologic Adverse Events

Adverse Event (Severity)	Action on Ixazomib	Action on Ibrutinib	Further Considerations
Grade 3 Non-Hematologic Toxicity	• Hold ixazomib until resolution to Grade ≤ 1 or baseline.	• NONE	**See Section 6.5.2 for dose reductions/modifications for toxicities related to ibrutinib.**
• If not recovered to ≤ Grade 1 or baseline within 2 weeks	• Reduce ixazomib to next lower dose upon return to ≤ Grade 1 or baseline (Table 6-5).	• NONE	
• Subsequent recurrence Grade 3 that does not recover to ≤ Grade 1 or baseline within 2 weeks	• Hold ixazomib until resolution to Grade <1 or baseline. • Reduce ixazomib to next lower dose (Table 6-5).	• NONE	Monitor closely, take appropriate medical precautions, and provide appropriate symptomatic care.
• Subsequent recurrence of Grade 3 toxicity that does not recover to ≤ Grade 1 despite treatment at lowest dose level of ixazomib (GI toxicities ONLY)	• Continue ixazomib at lowest dose	• For GI toxicities ONLY (nausea, vomiting, or diarrhea) reduce dose of ibrutinib to 420 mg daily.	In this setting, ibrutinib shall not be reduced below 420 mg daily. If a patient cannot tolerate the combination of ixazomib 2.3 mg and ibrutinib 420 mg, they shall be removed from study therapy.
Grade 4 Non-Hematologic Toxicity	• Consider permanently discontinuing ixazomib. • Discuss with PrECOG and principal investigator. • If it is felt to be of potential clinical benefit to reinitiate therapy, patients should be managed per the Grade 3 non-hematologic toxicity guidelines above.	• NONE	**See Section 6.5.2 for dose reductions/modifications for toxicities related to ibrutinib.** Exceptions are cases in which the investigator determines the patient is obtaining a clinical benefit. Patients who experience a recurrent grade 4 non-hematologic toxicity shall be permanently removed from study therapy.

Patients requiring a delay of 2 weeks or less before starting a cycle do not require a dose reduction unless a delay has been required on more than 1 cycle, in which case the ixazomib dose should be decreased by one level (Table 6-5).

The maximum delay before treatment should be discontinued will be 3 weeks or at the discretion of the principal investigator.

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 will be removed from the study.

Table 6-5 Recommended Dose Modifications for Ixazomib

	Starting Dose	Modification
Dose Level	4.0 mg	3.0 mg
Dose Level	3.0 mg	2.3 mg
Dose Level	2.3 mg	Remove from study

6.5.2 Additional Dose Reductions/Modifications for Ibrutinib

The following toxicities shall be considered related to ibrutinib and shall result in ibrutinib dose delay/modification per Table 6-6:

- Grade ≥ 3 Hemorrhage
- Grade ≥ 3 Hypertension
- Grade ≥ 3 Atrial Fibrillation
- Grade ≥ 3 Arthralgias

If a patient experiences any of these events, they should hold ibrutinib until recovery to grade ≤ 1 (or baseline) and subsequently shall modify the dose of ibrutinib as specified below in Table 6-6. The occurrence of any of these events does not require a dose adjustment/delay of ixazomib if the investigator feels that continued therapy is appropriate and concomitant toxicities do not require a dose delay/modification of ixazomib.

If at any time a patient experiences any grade ≥ 3 non-hematologic toxicity deemed at least possibly related to ibrutinib, the investigator should consider holding ibrutinib until the toxicity has resolved to grade ≤ 1 (or baseline). If upon resolution the toxicity is still felt to be at least possibly related to ibrutinib, patients should be restarted on ibrutinib according to the instructions in Table 6-6. An investigator may, at any time, permanently discontinue ibrutinib if they feel it is no longer safe to continue ibrutinib therapy. In this case, a patient may continue on ixazomib if felt to be benefitting from treatment. Any patient requiring discontinuation of ixazomib will be removed from study therapy.

Table 6-6: Dose Modifications for Ibrutinib

Occurrence	Action for Ibrutinib
First	Withhold ibrutinib until recover to grade ≤1 or baseline; may restart at original dose level.
Second	Withhold ibrutinib until recover to grade ≤1 or baseline; may restart at 420 mg/day.
Third	Withhold ibrutinib until recover to grade ≤1 or baseline; may restart at 280 mg/day (only for above ≥ Grade 3 toxicities).
Fourth	Discontinue ibrutinib.

Once a dose reduction of ibrutinib has occurred, there shall be no re-escalation of the ibrutinib dose in future cycles. Patients requiring discontinuation of ibrutinib may remain on study therapy with ixazomib alone if they are felt to be receiving clinical benefit and are otherwise eligible to continue study therapy. Patients requiring discontinuation of ixazomib will be removed from the study.

All toxicities (including ibrutinib-specific toxicities) shall be managed with appropriate supportive care and expert consultation as indicated. Patients may remain on study therapy if these are able to be medically managed and resolve to grade ≤ 1 with therapy. Anti-platelet therapy or anti-coagulation is allowed for patients experiencing atrial fibrillation as long as Warfarin is not used.

6.6 Concurrent Therapies

6.6.1 Required and/or Permitted

The following medications and procedures are permitted during the study:

- Antiemetics, including 5-HT3 serotonin receptor antagonists, may be used at the discretion of the investigator.
- Loperamide or other antidiarrheal should be used for symptomatic diarrhea at discretion of the investigator. The dose and regimen will be according to institutional guidelines. IV fluids should be given to prevent volume depletion.
- Growth factors (e.g., granulocyte colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF], recombinant erythropoietin) are permitted except for Cycle 1 of the phase 1 study (unless patient experiences a DLT). Their use should follow ASCO guidelines and/or institutional practice.
- Patients should be transfused with red cells and platelets as clinically indicated and according to institutional guidelines. However, transfusions may not be used to satisfy inclusion criteria for study entry.
- Antiviral therapy such as acyclovir may be administered if medically appropriate.
- Patients who experience worsening neuropathy from baseline may be observed for recovery, and have dose reductions/delays as indicated in the protocol, and any supportive therapy or intervention may be initiated as appropriate at the discretion of the investigator.
- Supportive measures consistent with optimal patient care may be given throughout the study.

6.6.2 Not Permitted

Strong CYP3A inducers should be avoided during treatment with ixazomib and/or ibrutinib:

- Avoid concomitant administration with strong CYP3A inducers (such as rifampin, phenytoin, carbamazepine, and St. John's Wort).

Systemic treatment with any of the above metabolizing enzyme inducers should be avoided, unless there is no appropriate alternative medication for the patient's use (Rationale: If there were to be a drug-drug interaction with an inducer, ixazomib and/or ibrutinib exposure would be decreased; therefore, there would be a reduced chance of an AE. However, there may be less chance for an antitumor effect, but that is not an absolute reason to be taken off ixazomib and/or ibrutinib).

Strong or moderate CYP3A inhibitors should be avoided during treatment with ibrutinib:

- Concomitant use of strong CYP3A inhibitors which would be taken chronically (e.g., ritonavir, indinavir, nelfinavir, saquinavir, boceprevir, telaprevir, nefazodone) is not recommended.
- For strong CYP3A inhibitors used short-term (e.g., antifungals and antibiotics for 7 days or less, e.g., ketoconazole, itraconazole, voriconazole, posaconazole,

clarithromycin, telithromycin) consider interrupting ibrutinib therapy during the duration of inhibitor use.

- Reduce ibrutinib to 140 mg if a moderate CYP3A inhibitor must be used (e.g., fluconazole, darunavir, erythromycin, diltiazem, atazanavir, aprepitant, amprenavir, fosamprenavir, crizotinib, imatinib, verapamil, and ciprofloxacin).
- Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A.

Patients taking concomitant strong or moderate CYP3A4 inhibitors should be monitored more closely for signs of ibrutinib toxicity.

The following procedures are prohibited during the study.

- Any antineoplastic treatment with activity against lymphoma, other than study drugs. This includes corticosteroids which should not be used with the intent to treat the underlying lymphoma for a patient who has initiated study therapy. Corticosteroid use as an anti-emetic or for other non-malignant etiologies may be used but should be limited to the smallest dose and duration required and should be documented.
- Radiation therapy (note that, in general, the requirement for local radiation therapy indicates disease progression).
- Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days prior to study drug dosing for any dosing day.
- Major surgery will be allowed as clinically indicated with a 7 day interruption of ibrutinib. Minor surgery will be allowed with a 3 day interruption of ibrutinib. Ixazomib does not have to be discontinued for surgery but one dose may be missed if the patient is unable to take the dose due to the surgery (or if the treating investigator feels it is in the patient's best interest to miss the dose). If more than one dose of ixazomib will need to be missed, this should be discussed with PrECOG.

7. Study Duration and Discontinuation of Therapy

7.1 Study Duration

Patients will receive protocol therapy unless:

1. Disease progression per LUGANO criteria or clinical progression.
2. Toxicities considered unacceptable by either the patient or the investigator, despite optimal supportive care and dose modifications.
3. Any requirement to discontinue ixazomib based on dose modification guidelines in Section 6.5.1.
4. Development of an inter-current illness that prevents further administration of study treatment.
5. Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued.
6. Patient withdraws consent or is unable to comply with study procedures.

7.2 Duration of Follow-Up

Patients will be followed for adverse events for 30 days after their last dose of study medication. However, if a patient experiences an adverse event >30 days after their last dose of study medication that is felt to be, in the opinion of the investigator, possibly, probably or definitely related to study therapy, the adverse event should be reported.

If a patient is removed from treatment for reason(s) other than progression, follow with regular tumor assessments per standard of care until progression or start of new treatment.

For patients who are registered but do not receive any protocol therapy, baseline and follow-up information per Section 10 will be collected.

7.3 Criteria for Removal from Study Treatment

A genuine effort will be made to determine the reason(s) why a patient fails to return for the necessary visits or is discontinued from the trial, should this occur. It will be documented whether or not each patient completed the clinical study. If for any patient study treatment or observations were discontinued, the reason will be recorded on the appropriate electronic case report form. Reasons that a patient may discontinue treatment in a clinical study are considered to constitute one of the following:

1. Recurrence of disease or documented progression of disease (with the exception of progressive lymphocytosis without any other evidence of disease progression).
2. Intercurrent illness that prevents further administration of treatment per investigator discretion.
3. Unacceptable adverse events and/or occurrence of dose limiting toxicity.
4. Treatment interruption of more than 3 weeks.
5. Investigator and/or patient discontinue chemotherapy.
6. Pregnancy.
7. Develops a second malignancy (except for non-melanoma skin cancer or cervical carcinoma in-situ) that requires treatment, which would interfere with this study.
8. The patient may choose to withdraw from the study at any time for any reason.
9. General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator.

10. Severe non-compliance to protocol as judged by the investigator.
11. Lost to follow-up.
12. Death.
13. Closure of study by PrECOG.

Any patient who receives at least one dose of ixazomib or ibrutinib will be included in the safety analysis. Patients who discontinue study treatment early should be followed for response assessments, if possible. Follow-up will continue per Section 10, as applicable.

8. Adverse Event Reporting

8.1 Collection of Safety Information

Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient administered a medicinal product in a clinical investigation and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a product (investigational or marketed), whether or not considered related to the product (investigational or marketed).

After informed consent, but prior to initiation of study treatment (ixazomib and ibrutinib), only AEs/SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as biopsies). After the initiation of study treatment, all identified AEs and SAEs must be recorded and described on the appropriate page of the electronic Case Report Form (eCRF). If known, the diagnosis of the underlying illness or disorder should be recorded, rather than individual symptoms. The following information should be documented for all AEs: date of onset and resolution, severity of the event; the investigator's opinion of the relationship to investigational product (see definitions below); treatment required for the AE treatment required for the AE; cause of the event (if known); and information regarding resolution/outcome.

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the eCRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more-frequent follow-up assessments, further diagnostic investigation, etc.).

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5x the ULN associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event eCRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the eCRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia".

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the eCRF unless their severity, seriousness, or etiology changes.

Severity

The categories and definitions of severity used for clinical trials AEs are defined in the NCI's Common Terminology Criteria (CTCAE) V5.0 (http://www.ctep.cancer.gov).

Attribution

The following categories and definitions of causal relationship or attribution to study drug should be used to assess Adverse Events:

- Definite: There is a reasonable causal relationship between the study drug and the event. The event response to withdrawal of study drug (dechallenge) and recurs with rechallenge, if clinically feasible.
- Probable: There is a reasonable causal relationship between the study drug and the event. The event responds to dechallenge. Rechallenge is not required.
- Possible: There is a reasonable causal relationship between the study drug and the event. Dechallenge information is lacking or unclear.
- Unlikely: There is doubtful causal relationship between the study drug and the event.

- Unrelated: There is clearly not a causal relationship between the study drug and the event or there is a causal relationship between another drug, concurrent disease, or circumstances and the event.

Categories 'definite', 'probable' and 'possible' are considered study drug related. Categories 'unlikely' and 'unrelated' are considered not study drug-related.

The development of a new cancer should be regarded as an AE. New cancers are those that are not the primary reason for administration of study treatment and have been identified after inclusion of the patient into the clinical study.

AEs related to ibrutinib and ixazomib should be followed for 30 days after last dose of study therapy until ≤ grade 1 or stabilization, and reported as SAEs if they become serious. Any AE's (serious or not) that occur more than 30 days after the last dose of study therapy but that are deemed to be at least possibly related to study therapy shall be reported.

8.2 Handling of Serious Adverse Events (SAEs)

8.2.1 SAE Definitions

A ***serious AE*** is any untoward medical occurrence occurring after initiation of study treatment or that at any dose:

- results in death,
- is life-threatening (defined as an event in which the study 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 causes prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect,
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above).

Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

8.3 SAE Reporting Requirements

Serious adverse events (SAE) are defined above. The investigator should inform PrECOG of any SAE within 24 hours of being aware of the event. The date of awareness should be noted on the report. This must be documented on the PrECOG SAE form. This form must be completed and supplied to PrECOG within 24 hours/1 business day at the latest on the following working day. The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up PrECOG SAE report form. A final report to document resolution of the SAE is required. The investigator is responsible for following all SAEs until resolution, until the subject returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation. A copy of the transmission confirmation of the SAE report to PrECOG should be attached to the SAE and retained with the patient records.

SAEs should be scanned and emailed to PrE0404SAE@qdservices.com as per the instructions found in study materials provided to the investigator site.

[redacted]
Medical Monitor
During normal business hours
(8:30 am-5:00 pm EST):
Phone: 610-354-0404
After normal business hours:
Phone: 484-574-2367
Email: [redacted]

Manager, Clinical Safety
During normal business hours
(8:30 am-5:00 pm EST):
Phone: 610-354-0404
After normal business hours:
Cell: 484-574-2367

PrECOG will notify Takeda Pharmacovigilance (or designee) of all SAE's within 24 hours of PrECOG's & Investigator's Awareness Date as discussed above. Relevant follow-up information will be provided to Takeda as soon as it becomes available.

Investigators should also report event(s) to their IRB as required.

Collection of complete information concerning SAEs is extremely important. Full descriptions of each event will be followed. Thus, follow-up information which becomes available as the SAE evolves, as well as supporting documentation (e.g., hospital discharge summaries and autopsy reports), should be collected subsequently, if not available at the time of the initial report, and immediately sent using the same procedure as the initial SAE report.

All SAEs, regardless of causality, must be collected which occur within 30 days of last dose of study treatment. This includes all deaths within 30 days of last dose of ixazomib and ibrutinib regardless of attribution. In addition, the Investigator should notify PrECOG or designee of any SAE that may occur after this time period which they believe to be definitely, probably or possibly related to investigational product.

NOTE: After study closure, study-drug related SAEs should be reported voluntarily by the treating physician to the manufacturer.

Serious adverse event reporting to regulatory authorities and all participating investigators will be conducted by PrECOG (or designee) in accordance with 21CFR312.32, local requirements and international regulations, as appropriate. FDA reporting requirement timelines will be followed. PrECOG will also concurrently forward any such reports to Takeda.

8.3.1 Product Complaints or Medication Errors

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. While overdoses and under doses constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential medication error situation should immediately contact PrECOG and report the event.

Product complaints and medication errors in and of themselves are not AEs. If a product complaint or medication error results in an SAE, an SAE form should be completed and sent to PrECOG.

8.4 Reporting of Other Second Primary Cancers

New cancers are those that are not the primary reason for administration of study treatment and have been identified after inclusion of the patient into the clinical study.

All cases of new primary cancers that occur during or after protocol treatment must be reported to PrECOG on a Second Primary Cancer form within 30 days of diagnosis, regardless of relationship to protocol treatment. Secondary primary malignancies should also be reported as a SAE. The SAE form is not for use for reporting recurrence or

development of metastatic disease. A copy of the pathology report, if applicable, should be sent, if available.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted.

8.5 Procedures in Case of Pregnancy

Prior to study enrollment, women of childbearing potential (WOCBP) and male patients with a female partner of childbearing potential must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy, documented in the informed consent. In addition, all WOCBP should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

Pregnancy of a female patient or the female partner of a male patient occurring while the patient is receiving study drug or within 3 months after the patient's last dose of study drug will be reported to PrECOG on a Pregnancy Form within 24 hours of the investigator's knowledge of the pregnancy.

All reports of congenital abnormalities/birth defects and spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth including health of the newborn or congenital abnormality) must be followed and documented on the Pregnancy Form even if the subject was discontinued from the study treatment. Should pregnancy occur during a subject's participation, the subject will immediately be discontinued from the treatment and followed per protocol.

The study-specific Pregnancy Form can be found in the Study Reference Manual.

9. Measurement of Effect

LUGANO Classification

All disease response evaluation shall occur according to the Lugano classification[35].

9.1 Scheduled Restaging Studies

All patients shall complete a PET/CT at the time of study enrollment. Thereafter, restaging shall include CT chest/abdomen/pelvis after cycles 3, 6, 9, and 12, and then every 6 months while on study therapy. PET/CT or MRI may be substituted for CT at the discretion of the treating investigator, especially in cases where lesions are not readily noted on CT. Patients who discontinue study therapy for reasons other than disease progression shall have CT's performed every 6 months until progression and/or initiation of a new therapy.

All patients with suspected CR based on routine restaging should have a PET/CT performed to confirm CR.

9.2 Complete Response (CR)

In order to satisfy the criteria for a complete response, patients who undergo CT scan only must meet the following criteria:

- Target nodes/nodal masses must regress to ≤1.5 cm in longest transverse diameter.
- No extralymphatic sites of disease.
- Absent non-measured lesions.
- All organ enlargement must be regressed to normal.
- No new lesions.
- Bone marrow must be normal by morphology (must be evaluated at the time of suspected CR in patients with a positive bone marrow at enrollment).

Patients undergoing a PET/CT must meet the following criteria:

- Deauville score of 1, 2 or 3 on the 5-point scale.
- No new lesions.
- No evidence of FDG avid disease in the bone marrow.

NOTE: ALL PATIENTS WITH SUSPECTED CR WHO HAD BONE MARROW INVOLVEMENT AT SCREENING MUST UNDERGO A BONE MARROW BIOPSY TO CONFIRM RESPONSE.

9.3 Partial Response (PR)

Patients undergoing a CT must meet the following criteria for PR:

- ≥ 50% decrease in the sum of the product of the diameters (SPD) of up to 6 target measurable nodes and extranodal sites.
- Lesions too small to measure on CT should be considered 5 mm x 5 mm as the default value.
- Lesions that are no longer visible should be considered 0 mm x 0 mm.
- Non-measured lesions should be absent/normal or regressed, but without increase.
- Spleen, if previously enlarged, must have regressed by >50% in length beyond normal.

Patients undergoing PET/CT must meet the following criteria for PR:

- Deauville score of 4 or 5 with reduced uptake compared to baseline and residual masses of any size.

- Bone marrow with residual uptake higher than uptake in normal marrow but reduced compared to baseline (diffuse uptake compatible with reactive changes from chemotherapy is allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan.

9.4 No Response/Stable Disease (SD)

Patients undergoing CT must meet the following criteria for SD/No response:

- <50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met.
- No increase of non-measured lesions or organ enlargement consistent with progression.

Patients undergoing PET/CT must meet the following criteria for SD/No response:

- Deauville score of 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment.
- No change in FDG activity of bone marrow from baseline.

9.5 Progressive Disease (PD)

Patients undergoing CT must meet one of the following criteria for PD:

- An individual node/lesion must be abnormal with the following:
  - Longest diameter >1.5 cm and
  - Increase by ≥ 50% from the cross product of the longest diameter and perpendicular diameter nadir and
  - Increase in the longest diameter or shortest diameter from nadir:
    - 0.5 cm for lesions ≤ 2 cm
    - 1.0 cm for lesions >2cm
- For patients with splenomegaly, the splenic length must increase by >50% of the extent of its prior increase above baseline. If no prior splenomegaly, it must increase by at least 2 cm from baseline.
- New or recurrent splenomegaly.
- New or clear progression of pre-existing non-measured lesions.
- Regrowth of previously resolved lesions.
- A new node >1.5 cm in any axis.
- A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma.
- Assessable disease of any size unequivocally attributable to lymphoma.
- New or recurrent bone marrow involvement.

Patients undergoing PET/CT must meet one of the following criteria for PD:

- Deauville score of 4 or 5 with an increase in intensity of uptake from baseline.
- New FDG-avid foci consistent with lymphoma (If uncertain regarding the etiology of a new lesion, biopsy or interval scan may be considered).

NOTE: Patients with isolated lymphocytosis shall not constitute progression in the absence of other findings.

9.6 Criteria for PET/CT Reporting

Patients who undergo PET/CT as part of their interim, on-treatment, and end of treatment staging assessments should be assessed according to the following scoring system.

1. No uptake above background.
2. Uptake ≤ mediastinum.
3. Uptake >mediastinum but ≤ liver.
4. Uptake moderately greater than liver.
5. Uptake markedly higher than liver and/or new lesions.

X New areas of uptake unlikely to be related to lymphoma.

For further information regarding the Deauville scoring system, please refer to Barrington et al, J Clin Oncol 2014[35].

10. Study Parameters

1. All pre-study scans should be done ≤ 4 weeks prior to registration.
2. All other pre-study assessments should be done ≤ 2 weeks prior to registration.

Procedures	Screening	Cycle 1* (1 cycle=28 Days)				Cycle 2-Cycle 6*				Cycle 7 and Subsequent Cycles[12]*	Every 3 Cycles*	Off Treatment[14]	Follow-Up[16]
		Day 1 +/- 1 day	Day 8 +/- 1 day	Day 15 +/- 1 day	Day 22	Day 1 +/- 3 days	Day 8 +/- 3 days	Day 15 +/- 3 days	Day 22 BREAK	Day 1 Every 12 Weeks			
Written Informed Consent	X												
Disease Characteristics[1]	X												
Medical/Surgical History	X												
Assessment of Baseline Signs & Symptoms	X												
Height	X												
Physical Exam including Weight	X	X		X		X				X[12]		X	
Vital Signs (Temperature, Pulse, Blood Pressure)	X	X		X		X				X[12]		X	
Performance Status	X	X				X				X[12]		X	
CBC/Differential/Platelets[2]	X	X		X	X	X[2]		X[2]		X[2]		X	
Chemistry[3]	X	X		X		X[3]				X[3]		X	
PT/INR	X												
Lactate Dehydrogenase (LDH)	X												
Vitamin D Level[4]	X												
Peripheral Blood Flow Cytometry	X												
Serum Pregnancy Test[5]	X												
PET/CT	X												
Chest/Abdomen/Pelvic MRI or CT[6]											X[13]	X	
Bone Marrow Aspirate and Biopsy[7]	X											X[7]	

Procedures	Screening	Cycle 1* (1 cycle=28 Days)				Cycle 2-Cycle 6*				Cycle 7 and Subsequent Cycles[12]*	Every 3 Cycles*	Off Treatment[14]	Follow-Up[16]
		Day 1 +/- 1 day	Day 8 +/- 1 day	Day 15 +/- 1 day	Day 22	Day 1 +/- 3 days	Day 8 +/- 3 days	Day 15 +/- 3 days	Day 22 BREAK	Day 1 Every 12 Weeks			
Bone Marrow Conventional Cytogenetics and FISH[8]	X												
Pathology Review with Ki67 Assessment[9]	X												
Research Specimens[10]		X[10]									X[10]	X[10]	
Treatment Administration[11]		X	X[11]	X		X[11]	X[11]	X[11]		X[11]			
Concomitant Medication Review	X	X		X		X				X[12]		X	
Adverse Events Assessment		X		X		X				X[12]		X[15]	
Survival Status													X

* **Scheduled Visits:** +/-3 day window is allowed for scheduled ixazomib therapy, required tests and/or visits except as otherwise noted. Delay due to holidays, weekends, bad weather or other unforeseen circumstances will be permitted.

1 Record date of diagnosis and stage.

2 CBC with differential and platelet count which includes WBC, ANC, Platelets, Hemoglobin, and Hematocrit required as noted below.

Phase I: Days 1, 8, 15 and 22 of Cycle 1; Days 1 and 15 of Cycle 2 and Cycle 3 (patients with ANC <1000 and/or platelets <100,000/mm^3 on Day 15 should have blood counts done on Day 22 for Cycle 2 and 3 only); and Day 1 of subsequent cycles. **Phase I completed November 25, 2019.**

Phase II: Days 1 and 15 of Cycle 1 for which a clinic visit is required. Patients will be required to be seen in clinic on Day 1 of Cycles 2-7, then every 3 cycles thereafter. Labs are only required on the days patients are seen in clinic.

Results known prior to treatment administration. Patients experiencing cytopenias should have additional labs drawn as clinically indicated at the discretion of the treating physician.

3 Albumin, BUN/creatinine, uric acid, sodium, potassium, chloride, glucose, calcium, alkaline phosphatase, AST, ALT, total bilirubin, and total protein. Days 1 and 15 of Cycle 1 for which a clinic visit is required. Patients will be required to be seen in clinic on Day 1 of Cycles 2-7, then every 3 cycles thereafter. Labs are only required on the days patients are seen in clinic.

NOTE: Patients with a history of hepatitis B or C must have a negative peripheral blood Polymerase Chain Reaction (PCR) and may not be positive for Hepatitis B surface antigen.

4 25(OH) Vitamin D level.

5 Required for sexually active females of child-bearing potential.

6 PET/CT may be substituted for CT Chest/Abdomen/Pelvis at the discretion of the investigator.

7 Bone Marrow Biopsy to include: Aspirate and core biopsy morphologic evaluation and flow cytometry. Bone marrow biopsy will be repeated at the time of suspected CR for patients with involvement at the time of enrollment. Optional bone marrow biopsies and aspirates will be performed as clinically indicated at the end of therapy and/or time of progression.

8 Bone marrow samples will be sent for conventional cytogenetics, FISH for t(11;14) and FISH for del(17p) [conventional cytogenetics, FISH for t(11;14) and FISH for del(17p) may also be done on tumor tissue samples (nodal or extranodal) in lieu of or in addition to bone marrow review].

9 Pathologists at the participating site must review available tissue samples to confirm the diagnosis of MCL. If a pathology review has already been completed in the routine care of the patient, then additional review is not required. All patients should have an assessment of Ki67 performed on available tissue. Tissue used for pathology review should ideally be from the time of relapse but pre-treated tissue can be used if that is the only available sample.

10 Research samples shall be obtained at the time of screening/study entry, after cycle 3, at time of suspected CR, and at the end of therapy or time of progression. Refer to Section 13 for details.

Screening/Study Entry
Peripheral Blood: Two 6 mL in EDTA tubes
Bone Marrow: One 10 mL in EDTA tube
FFPE: Block preferred or 1 H&E slide plus 10 unstained slides

After Cycle 3 (up to 5 days before Cycle 4, Day 1)
Peripheral Blood: Two 6 mL in EDTA tubes

At time of Suspected CR
Peripheral Blood: Two 6 mL in EDTA tubes

End of Therapy/At Time of Progression (within 45 days of last dose of study medication)
Peripheral Blood: Two 6 mL in EDTA tubes

NOTE: If sufficient bone marrow and tumor tissue are available, submission is mandatory). No bone marrow biopsy/aspirate or tissue biopsy should be performed solely for the purposes of obtaining research samples.

11 Patients will receive ixazomib orally on days 1, 8, and 15 of each 28 day cycle (1 cycle=28 days) [Section 6.1.1 for dosing administration]. Ixazomib shall be administered in the clinic on Cycle 1, Day 1 and Cycle 1, Day 15 (Day 8 can be administered at home). For subsequent cycles, ixazomib doses on Days 8 and 15 can be administered at home. Ixazomib Medication Diary will be reviewed for compliance and collected every cycle after Cycle 1 (Appendix III). Ibrutinib shall be administered orally daily on days 1-28 [Section 6.1.2 for dosing administration]. Ibrutinib Medication Diary will be reviewed for compliance and collected every cycle (Appendix IV). See Section 6.2 for Phase I and Section 6.3 for Phase II dosing instructions and Section 6.5 for dose delays/modifications.

NOTE: If patient continues on study therapy after Cycle 6, the visit schedule may be increased to every 3 cycles starting with Cycle 7 and study medication will be dispensed for 3 cycles. Medication Diaries will be collected every 3 cycles when patient returns to clinic.

12 If patient continues on study therapy after Cycle 6, the visit schedule may be increased from 4 to 12 weeks starting with Cycle 7 while receiving study therapy (Scan schedule will remain unchanged, see footnote 13). Physical exam with weight, vital signs, performance status, blood work, concomitant medication review and adverse events assessment will be performed every 12 weeks (Day 1 of every 3 cycles).

13 While on treatment, patients shall undergo CT chest/abdomen/pelvis (or PET/CT or MRI as clinically indicated per investigator discretion) after cycles 3, 6, 9, 12 and subsequently every 6 months while on study therapy. Scans should be performed during the 7 days preceding the following cycle (i.e., within 7 days of Cycle 4, Day 1). **Patients with suspected CR should undergo PET/CT to confirm this. This can be done within 21 days of the restaging CT that initially demonstrates potential CR.**

14 Thirty (30) days +/- 7 days after last dose of study therapy. If patient is removed from treatment for reason(s) other than progression, follow with regular tumor assessments per standard of care until progression or start of new treatment. Once a patient has initiated a new therapy, no further study-related imaging assessments for this study are required.

15 Patients will be followed for adverse events for 30 days after their last dose of study medication. However, an adverse event occurring at any time after discontinuation of study therapy that is felt to be at least possibly related to study therapy should be recorded.

16 There are no study-related visits required after the end of treatment visit. However, as available to the participating investigators, survival status every 6-12 months for participating patients should be updated and recorded. In addition, the first subsequent therapy shall be reported.

11. Drug Formulation and Procurement

11.1 Ixazomib[36]

11.1.1 Other Names

Ixazomib is also referred to as MLN9708 or MLN2238.

11.1.2 Classification

Ixazomib is an oral proteasome inhibitor.

11.1.3 Storage and Stability

Upon receipt at the investigative site, ixazomib should remain in the blister and carton provided until use or until drug is dispensed. The container should be stored at the investigative site; do not store above 86°F (30°C); do not freeze. Ensure that the drug is used before the retest expiry date provided. Expiry extensions will be communicated accordingly with updated documentation to support the extended shelf life.

Ixazomib capsules dispensed to the patient for take-home dosing should remain in the blister packaging and refrigerated as noted above until the point of use. The investigative site is responsible for providing the medication to the patient in the correct daily dose configurations. Comprehensive instructions should be provided to the patient in order to ensure compliance with dosing procedures. Patients who are receiving take-home medication should be given only 1 cycle of medication at a time (starting with Cycle 7, may receive 3 cycles at a time). Patients should be instructed not to store the medication above 86°F (30°C); do not freeze for the duration of each cycle. Patients should be instructed to return their empty blister packs to the investigative site, rather than discarding them. Reconciliation will occur accordingly when the patient returns for their next cycle of take-home medication. Any extreme in temperature should be reported as an excursion and should be dealt with on a case-by-case basis.

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

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

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

11.1.4 Dose Specifics

Ixazomib is dispensed in a 4-week supply (starting with Cycle 7, may be dispensed in 12-week supply). The capsules will be individually packaged using cold-form foil-foil blisters that are in child-resistant carton. There will be 3 capsules in each wallet/carton. Patients will take one capsule on days 1, 8, and 15 of each cycle.

Refer to Section 6.5.1 and Table 6-3, Table 6-4 and Table 6-5 for Dose Delays and Modifications details.

11.1.5 Route of Administration

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

Missed doses can be taken as soon as the patient remembers if the next scheduled dose is 72 hours or more away for all cycles aside from Cycle 1 of the phase 1 portion of the study. Patients with dose delays in Cycle 1 shall be managed as described in Section 6.2. A double dose should not be taken to make up for a missed dose. If the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose.

Ixazomib Medication Diary will be reviewed for compliance and collected every cycle for Cycle 1-Cycle 6 (Appendix III). Starting with Cycle 7, Ixazomib Medication Diary will be reviewed and collected every 3 cycles.

11.1.6 Drug Interactions

Avoid concomitant administration of ixazomib with strong CYP3A inducers (such as rifampin, phenytoin, carbamazepine, and St. John's Wort).

11.1.7 Agent Availability

Ixazomib capsules will be supplied by Takeda Pharmaceuticals.

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

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

The initial supply of ixazomib will be sent directly to the site upon site activation. As needed, ixazomib may be requested by the principal investigator (or their authorized designees) at each participating institution. The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return/destruction (site's drug destruction policy must be reviewed and approved by PrECOG before any study drug can be destroyed at a site) of ixazomib.

11.1.8 Agent Ordering

PrECOG will be responsible for ordering drug for re-supply to the site. Requests for shipments of ixazomib will be coordinated between PrECOG and Takeda.

11.1.9 Agent Accountability

Ixazomib will be stored in a secure location. Only authorized pharmacy and study staff will have access to this agent. Drug accountability will be performed by PrECOG.

11.1.10 Side Effects

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

11.1.10.1 Prophylaxis Against Risk of Reactivation of Herpes Infection

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

11.1.10.2 Nausea and/or Vomiting

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

11.1.10.3 Diarrhea

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

11.1.10.4 Erythematous Rash With or Without Pruritus

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

Symptomatic measures such as antihistamines or corticosteroids (oral or topical) have been successfully used to manage rash and have been used prophylactically in subsequent cycles. The use of a topical, IV, or oral steroid (e.g., prednisone ≤ 10 mg per day or equivalent) is permitted. Management of a Grade 3 rash may require intravenous antihistamines or corticosteroids. Administration of ixazomib (and/or other causative agent if given in combination) should be modified per protocol and re-initiated at a reduced level from where rash was noted (Table 6-4).

In line with clinical practice, dermatology consult and biopsy of Grade 3 or higher rash or any SAE involving rash is recommended. Prophylactic measures should also be considered if a patient has previously developed a rash (e.g., using a thick, alcohol-free emollient cream on dry areas of the body or oral or topical antihistamines). Rare risks are Stevens-Johnson Syndrome, a severe and potentially life-threatening rash with skin peeling and mouth sores, toxic epidermal necrolysis (TEN) and drug

reaction with eosinophilia and systemic symptoms (DRESS syndrome) which should be managed symptomatically according to standard medical practice. Punch biopsies for histopathological analysis are encouraged at the discretion of the investigator.

11.1.10.5 Thrombocytopenia

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Thrombocytopenia may be severe but has been manageable with platelet transfusions according to standard clinical practice. Ixazomib administration should be modified as noted as per dose modification recommendations in the protocol when thrombocytopenia occurs (Table 6-3). Therapy can be reinitiated at a reduced level upon recovery of platelet counts. A rare risk is thrombotic thrombocytopenic purpura (TTP), a rare blood disorder where blood clots form in small blood vessels throughout the body characterized by thrombocytopenia, petechiae, fever, or possibly more serious signs and symptoms. TTP should be managed symptomatically according to standard medical practice.

11.1.10.6 Neutropenia

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Neutropenia may be severe but has been manageable. Growth factor support is not required but may be considered according to standard clinical practice. Ixazomib administration should be modified as noted as per dose modification recommendations in the protocol when neutropenia occurs (Table 6-3). Therapy can be reinitiated at a reduced level upon recovery of ANCs.

11.1.10.7 Fluid Deficit

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

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

11.1.10.8 Hypotension

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

11.1.10.9 Posterior Reversible Encephalopathy Syndrome

One case of posterior reversible encephalopathy syndrome, which ultimately resolved, has been reported with ixazomib. This condition is characterized by headache, seizures and visual loss, as well as abrupt

increase in blood pressure. Diagnosis may be confirmed by magnetic resonance imaging (MRI). If the syndrome is diagnosed or suspected, symptom-directed treatment should be maintained until the condition is reversed by control of hypertension or other instigating factors.

11.1.10.10 Transverse Myelitis

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

11.2 Ibrutinib[37]

11.2.1 Other Names

Additional names for ibrutinib include Imbruvica® and PCI-32765.

11.2.2 Classification

Ibrutinib is an oral inhibitor of Bruton's tyrosine kinase. **Ibrutinib is approved for the treatment of patients with Mantle Cell Lymphoma and will be obtained commercially.**

11.2.3 Mode of Action

Ibrutinib is a small-molecule inhibitor of BTK. Ibrutinib forms a covalent bond with cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. BTK's role in signaling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis, and adhesion. Nonclinical studies show that ibrutinib inhibits malignant B-cell proliferation and survival in vivo as well as cell migration and substrate adhesion in vitro.

11.2.4 Storage and Stability

Ibrutinib is provided as white opaque 140 mg capsules marked with "ibr 140 mg" in black ink. Bottles should be stored at room temperature 20°-25°C (68°-77°F). Excursions are permitted between 15°C and 30°C (59°F to 86°F).

11.2.5 Dose Specifics

Ibrutinib shall be obtained through available commercial pharmacies. Patients should take the dose as prescribed by the treating investigator, with a maximum dose of 560 mg (4 tablets). Doses should be taken at the same time each day. Ibrutinib should be swallowed whole with water and the tablets should not be opened, broken, or chewed. If a dose of ibrutinib is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. Extra capsules of ibrutinib should not be taken to make up for the missed dose.

Refer to Section 6.5.2 and Table 6-6 for Dose Delays and Modifications details.

11.2.6 Route of Administration

Ibrutinib shall be consumed orally, with the full capsules swallowed for each dosing. Ibrutinib Medication Diary will be reviewed for compliance and collected every cycle for Cycle 1-6 [Appendix IV]. Starting with Cycle 7, Ibrutinib Medication Diary will be reviewed and collected every 3 cycles.

11.2.7 Drug Interactions

Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A.

11.2.7.1 CYP3A Inhibitors

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 such as ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin) consider interrupting ibrutinib until the CYP3A inhibitor is no longer needed. Reduce ibrutinib to 140 mg if a moderate CYP3A inhibitor must be used (e.g., fluconazole, darunavir, erythromycin, diltiazem, atazanavir, aprepitant, amprenavir, fosamprenavir, crizotinib, imatinib, verapamil, and ciprofloxacin).

Patients taking concomitant strong or moderate CYP3A4 inhibitors should be monitored more closely for signs of ibrutinib toxicity.

Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A.

11.2.7.2 CYP3A Inducers

Administration of ibrutinib with rifampin, a strong CYP3A inducer, decreased ibrutinib C_{max} and AUC by approximately 13- and 10-fold, respectively.

Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin and St. John's Wort). Consider alternative agents with less CYP3A induction.

11.2.8 Availability

Ibrutinib shall be obtained through commercial or other sources and shall not be provided by the study.

11.2.9 Side Effects

There are no listed contra-indications for ibrutinib.

11.2.9.1 Hemorrhage

Fatal bleeding events have occurred in patients treated with ibrutinib. Grade 3 or higher bleeding events (subdural hematoma, gastrointestinal bleeding, hematuria and post procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with ibrutinib.

The mechanism for the bleeding events is not well understood.

Ibrutinib may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies.

Consider the benefit-risk of withholding ibrutinib for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding.

11.2.9.2 Infections

Fatal and non-fatal infections have occurred with ibrutinib therapy. Grade 3 or greater infections occurred in 14% to 26% of patients. Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with ibrutinib. Monitor patients for fever and infections and evaluate promptly.

11.2.9.3 Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 19 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 9%) occurred in patients treated with ibrutinib.

11.2.9.4 Atrial Fibrillation

Atrial fibrillation and atrial flutter (range, 6 to 9%) have occurred in patients treated with ibrutinib, particularly in patients with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness) or new onset dyspnea should have an ECG performed. If atrial fibrillation persists, consider the risks and benefits of ibrutinib treatment and dose modification.

11.2.9.5 Second Primary Malignancies

Other malignancies (range, 5 to 14%) including non-skin carcinomas (range, 1 to 3%) have occurred in patients treated with ibrutinib. The most frequent second primary malignancy was non-melanoma skin cancer (range, 4 to 11 %).

11.2.9.6 Tumor Lysis Syndrome

Tumor lysis syndrome has been reported with ibrutinib therapy. Monitor patients closely and take appropriate precautions in patients at risk for tumor lysis syndrome (e.g. high tumor burden).

11.2.10 Nursing/Patient Implications

Based on findings in animals, ibrutinib can cause fetal harm when administered to a pregnant woman. Ibrutinib caused malformations in rats at exposures 14 times those reported in patients with MCL and 20 times those reported in patients with Chronic Lymphocytic Leukemia or Waldenström's Macroglobulinemia, receiving the ibrutinib dose of 560 mg per day and 420 mg per day, respectively. Reduced fetal weights were observed at lower exposures. Advise women to avoid becoming pregnant while taking ibrutinib. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

Women who are nursing are not eligible for this study and any woman who becomes pregnant over the course of the study will be removed from study therapy.

Ibrutinib is a Pregnancy Category D drug.

Please refer to the commercial package insert for full prescribing information.

12. Statistical Considerations

12.1 Study Design & Sample Size Considerations

This study will be conducted in two phases: Phase I and Phase II. The phase I portion will include dose-escalation and de-escalation designed to identify the RP2D/MTD for the combination of ixazomib and ibrutinib for the phase II portion of the study. Based on the planned dose escalation and de-escalation described below, we will enroll a minimum of 6 patients (assuming DLT on levels 1 & -1) and a maximum of 12 patients (assuming 6 patients accrued to two dose levels) on the phase I portion of the study.

Phase I Summary: Three patients were enrolled to Dose Level 1 with no DLTs during the 28 day assessment period. Nine patients were enrolled to Dose Level 2. Five of the nine patients completed the 28 day assessment period with no DLTs. One patient experienced a DLT. Three of the nine patients were not evaluable for DLT and were replaced. One patient was inadvertently given neulasta prior to receiving Cycle 2, Day 1 therapy; another patient unintentionally took Day 15 ixazomib on Day 9; and one patient forgot to take ibrutinib the last 8 days of Cycle 1 unrelated to any toxicities. **Phase I was completed November 25, 2019. Dose Level 2 is the recommended Phase 2 dose.**

12.1.1 Phase I

For the phase I portion of the study, the primary objective will be to evaluate safety and toxicity of ixazomib when administered in combination with ibrutinib for patients with relapsed/refractory MCL, which we will assess by determining the MTD/RP2D as described in Section 6.2.1. We will determine this using a standard 3+3 design. The first cohort of 3 patients will be accrued to Dose Level 1 and will start therapy with ixazomib and ibrutinib. These 3 patients will be evaluated for a DLT during the first 28-day cycle, with DLT defined according to Table 6-2. If zero patients experience a DLT, the next cohort of 3 will be accrued at the next dose level. If 1 patient experiences a DLT, the next cohort of 3 will be accrued at the same dose level to further evaluate safety. If 2 or 3 patients experience a DLT, that level will be deemed too toxic and next cohort of 3 will be accrued to Dose Level (-1). If Dose Level (-1) proves too toxic, the study will end. If 1 or fewer out of 6 patients experience a DLT, then that level will be deemed the RP2D and the phase I trial will end.

Dose Level	**Ixazomib Days 1, 8, 15 of a 28 Day Cycle**	**Ibrutinib Days 1-28 of a 28 Day Cycle**
-1	3 mg	420 mg
1 **Starting Dose**	3 mg	560 mg
2	4 mg	560 mg

The table below summarizes the probabilities of dose escalation and de-escalation for a range of true DLT rates for the combination treatment using the standard 3+3 design.

	True DLT Rate							
	1%	5%	10%	15%	20%	30%	40%	50%
Probability of Dose escalation	.999	.973	.906	.814	.709	.494	.309	.172
Probability of Dose de-escalation	.001	.027	.094	.186	.291	.506	.691	.828

12.1.2 Phase II

For the phase II portion of the study, we will accrue patients to two cohorts (BTK-naïve [Cohort A] and BTK-pretreated [Cohort B]) simultaneously. The primary endpoint for the phase II study will be the CR rate, with planned comparison to historical controls. The target CR rate for the BTK-naïve cohort will be 40%, based on a historical rate of 21% for single agent ibrutinib, and the target CR rate for the BTK-pretreated cohort will be 23% based on a single agent CR rate of 8% for bortezomib. As a result, we will accrue 31 eligible, treated patients to each cohort for a total of 62 eligible, treated patients for the phase II study. To assure an adequate number of eligible, treated patients, up to 36 patients will be enrolled to each arm.

12.1.2.1 Administrative Changes: August 7, 2020

Due to administrative and/or industry sponsor reasons, it was decided that enrollment to Cohort B (BTK-pretreated cohort) will be stopped. The total number of BTK-pretreated patients enrolled was 2 as of August 7, 2020.

Enrollment to Cohort A (BTK-naïve cohort) will continue however, and up to the full accrual of 36 patients as initially planned. To supplement the enrollment of 36 patients in Cohort A, the BTK-naïve patients that were treated at the R2PD in Phase I (n=6) will contribute to the 36 patients needed for full accrual in Phase II.

The statistical operating characteristics, and primary endpoint, of the BTK-naïve cohort remains the same as indicated in Section 12.1.2 above.

12.2 Phase II

12.2.1 Primary Objectives

Patients will receive oral ixazomib and ibrutinib, in combination, at the RP2D. The efficacy of ixazomib and ibrutinib therapy will be assessed using CR rate. The CR rate will be the defined as the percentage of patients who achieve a CR (confirmed by BM biopsy) within the first 12 months of initiating treatment. Patients who are unevaluable or whose CR is not confirmed by BM biopsy will be included in the denominator as non-responders when computing the CR rate. Relapse/progression will be defined as either frank progression by clinical or laboratory exam (i.e., increased circulating monoclonal lymphocytes) or progressive disease by restaging CT, defined according to standard criteria.[34] Patients with isolated lymphocytosis shall not constitute progression in the absence of other findings.

In order to facilitate rapid accrual and to determine evidence of efficacy in multiple clinical settings, patients in the phase II portion of the study will be divided into two cohorts. Cohort A will include BTK-naïve patients. Cohort B will include BTK-pretreated patients. **August 7, 2020: BTK-pretreated cohort closed.**

Based on a historical single-agent 21% CR rate of ibrutinib in relapsed/refractory MCL[4], we would consider a CR rate of 40% for the combination therapy in the BTK-naïve cohort (Cohort A) to be of interest. To detect an improvement of CR rate to 40% from the historical CR rate of 21%, a total of 31 patients will be accrued to Cohort A. This design will have 86% power and 10% one-sided Type I error using an exact binomial test and the null hypothesis will be rejected if CR is observed in 10 or more patients.

For the BTK-pretreated cohort (Cohort B) a CR rate of 23% will be of interest and a CR rate of 8%, based on a previously reported single agent CR rate for bortezomib, will not be of interest. To detect an improvement in CR rate to 23% from 8%, a total of 31 patients will also be accrued to Cohort B. This design will have 87% power and

10% one-sided Type I error using an exact binomial test and the null hypothesis will be rejected if CR is observed in 5 or more patients. **August 7, 2020: BTK-pretreated cohort closed.**

12.2.2 Secondary Objectives

The secondary objectives for phase I and II of this study will include evaluation of regimen-related toxicities for the combination of ixazomib and ibrutinib in relapsed/refractory MCL; evaluation of the ORR for the drug combination; and to evaluate the median PFS and OS for patients treated with the drug combination.

To describe the ORR for phase I and II, descriptive statistics will be used to compute the proportion of patients who achieved complete and partial response to the drug combination. A 90% exact binomial confidence interval (CI) around the overall response rate estimate from the phase II portion of this study will be computed for descriptive purposes. Based on the planned dose escalation and de-escalation, between 6 and 12 patients will be accrued to the phase I portion of this study.

The median PFS and OS will be evaluated using the Kaplan Meier method, separately for phase I and II patients. The estimates from the phase I will give preliminary information about efficacy which will be further assessed in the phase II patients. The patients included in survival efficacy analysis will include eligible and treated patients only.

All enrolled patients who receive treatment, irrespective of eligibility, will be reviewed for toxicities attributable to treatment. The phase I assessment of treatment-related toxicities of Grade 3 or higher will be described using proportions. In phase II, if 72 patients (up to 36 in each cohort; **August 7, 2020: BTK-pretreated cohort closed.**) are treated and assuming there is an equal rate of toxicity in both cohorts, the maximum width of 90% CI on the proportion of treatment-related grade 3 or higher toxicity in both cohorts, combined, will be no wider than 20%. The probability of observing at least one rare toxicity (true rate of 5%) is approximately 97.5%. **August 7, 2020:** Among 36 treated patients, the maximum 2-sided width of a 90% CI around the proportion of treatment related Grade 3 or higher toxicity will be within 29.4% and the probability of seeing ≥1 rare toxicity if such toxicity has a true prevalence of 5% for example is 84.2%.

We will also describe and tabulate all adverse events, regardless of treatment attribution.

To assure an adequate number of eligible, treated patients, up to 36 patients will be enrolled to each arm. This will result in a maximum accrual of 84 patients for the full study (**August 7, 2020: BTK-pretreated cohort closed; updated per Section 12.1.2.1)**.

The efficacy assessment population will include all eligible and treated patients while the adverse events assessment population will include all treated patients, regardless of eligibility.

12.3 Planned Analyses

12.3.1 Toxicity Monitoring Plan

Toxicity and adverse events for all enrolled patients will be monitored throughout the conduct of the study. For the phase I portion of the study, all patients will be evaluated for the development of a DLT as defined in Section 6.2.1. Those patients experiencing a DLT shall be removed from study therapy and the dosing for subsequent cohorts of patients shall be adjusted as described in the protocol.

All other toxicities or adverse events encountered for all patients from the time of study treatment initiation (any toxicities or adverse events related to a protocol-mandated intervention after informed consent is signed will also be included) until the withdrawal of consent or the patient has been off study therapy for 30 days shall be reported, regardless of attribution. We shall review all reported adverse events and shall present recurrent adverse events, grade 3-5 adverse events, or other adverse events felt to be clinically significant and related to study therapy in tabular form.

In addition to the planned tabular description of encountered adverse events, PrECOG shall convene a data safety monitoring board to review the safety of all enrolled patients and ensure compliance with all appropriate guidelines.

12.3.2 Analyses of Correlative Studies

13. Laboratory and Pathology Correlative Studies

13.1 Correlative Studies

13.1.1 Overview

In addition to the planned primary assessments of safety/tolerability and efficacy of the combination, we will also evaluate several candidate predictive and prognostic biomarkers in MCL through analysis of mandatory collected tissue samples, bone marrow aspirates, and peripheral blood. In addition, patient samples collected at pre-specified time points shall be sent to the ECOG-ACRIN Central Biorepository Pathology Facility (E-A CBPF) to be stored and used for future study.

Several of the planned analyses shall take place at the local site under the supervision of the treating investigators while others shall be conducted centrally through the use of the repository.

NOTE: If sufficient bone marrow and tumor tissue are available, submission is mandatory. No bone marrow biopsy/aspirate or tissue biopsy should be performed solely for the purposes of obtaining research samples.

13.1.2 Methodology

Local Assays:

Ki67 Proliferative Index: The Ki67 proliferative index shall be assessed for all tumor samples used to confirm the diagnosis of relapsed MCL for the purposes of this study. This shall be conducted according to each institutional practice and shall be reported as a percentage of cells expressing Ki67. This shall occur at one time point at the time of study entry. Patients for whom there is no tissue available to conduct this assessment will **NOT** require repeat biopsies simply for the purposes of conducting this assessment.

Cytogenetic Analyses: Each site shall submit a bone marrow aspirate sample and/or a tumor tissue sample (nodal or extranodal) for cytogenetic assessments. These assessments shall be conducted locally according to institutional standards. In addition to a conventional cytogenetic assessment, samples shall be assessed by FISH for t(11;14) and FISH for del(17p). Patients shall require 1 (one) sample (either from the bone marrow or from involved tissue) with preference given towards using a sample that is known to be involved with MCL.

Vitamin D Level Assessment: All patients at the time of study enrollment will have a 25(OH) Vitamin D3 level drawn by peripheral blood draw. This one-time assessment will be processed locally.

Centrally Processed Assays:

Peripheral blood and involved tissue samples shall be sent to a central lab for future use. Planned assessments include the following:

PSMB1 Allele Frequency: Given the potential association of the PSMB1 P11A (G allele) with prolonged PFS and OS in patients treated with bortezomib, we will assess the allelic frequency among enrolled patients. All patients will provide a peripheral blood sample at the time of enrollment that will be utilized to evaluate allelic frequency. This shall be determined using a TaqMan SNP assay.

BTK Mutational Analysis: All patients will have a mutational analysis of BTK and PLC-γ2 performed on involved tissue samples. This will be performed using the commercially available NeoGenomics assay and will require Formalin-Fixed, Paraffin-Embedded (FFPE) tissue or bone marrow from aspirate.

Future studies: We will collect and store samples for future correlative studies and will be incorporated into this protocol as future amendments as they are developed.

13.1.3 Sample Collection

Kits will be supplied for research samples. Instructions will be provided in the kit.

Planned research assessments and required submissions:

Screening/Study Entry

Local, per Institutional Practice

- Ki67 assessment
- Conventional cytogenetics
- FISH for t(11;14)
- FISH for del(17p)
- 25(OH) Vitamin D

Research Samples

- Peripheral Blood: Two 6 mL in EDTA tubes
- BM aspirate: 10 mL in EDTA tube
- Formalin-Fixed, Paraffin-Embedded (FFPE) tissue (block preferred or 1 H&E slide plus 10 unstained slides)

After Cycle 3

Up to 5 days before Cycle 4, Day 1
Peripheral Blood: Two 6 mL in EDTA tubes

Suspected CR

At Time of Suspected CR
Peripheral Blood: Two 6 mL in EDTA tubes

End of Therapy/At Time of Progression

Within 45 days of last dose of study medication

- Peripheral Blood: Two 6 mL in EDTA tubes

NOTE: If sufficient bone marrow and tumor tissue are available, submission is mandatory. No bone marrow biopsy/aspirate or tissue biopsy should be performed solely for the purposes of obtaining research samples.

13.1.4 Research Samples Processing and Shipment

Instructions, shipping labels, supplies and address will be provided in the kits.

All samples collected will be labeled with a unique numeric identifier that will be coded for patient privacy protection.

13.1.4.1 FFPE Tissue Block or Slide Samples

Sites should submit FFPE tumor tissue blocks or FFPE slides (2 sections per slide) plus H&E slide from a tumor tissue block as noted in Section 13.1.3. Thickness of the sections should be at 4-5 micron. Screening/Study Entry samples should be submitted within 1 month of patient registration.

A copy of the pathology report should be sent when the sample is shipped. Samples should be shipped **Monday-Thursday**. Samples will be shipped ambient via overnight courier.

13.1.4.2 Bone Marrow (BM) Samples

Sites should submit BM samples in EDTA tubes as noted in Section 13.1.3.

Store in the freezer at ≤ -70°C or colder until shipped to central lab.

BM samples should be submitted within 4 months of obtaining, as applicable. A copy of the BM report should be sent when the sample is shipped. Samples should be shipped **Monday-Thursday**. Samples must be shipped on dry ice via overnight courier.

13.1.4.3 Peripheral Blood Samples

Sites should submit peripheral blood samples in EDTA tubes as noted in Section 13.1.3.

EDTA Tube Processing for Plasma and Buffy Coat

****Process sample within 30 minutes of collection****

- Gently mix blood sample by inversion 10 times (do not shake).
- Place tube immediately on wet ice for 5 minutes.
- Centrifuge at 1200 RPM for 15 minutes at 4°C. If a refrigerated centrifuge is not available, spin sample at room temperature (1200 RPM for 15 minutes). Immediately place the tube on wet ice after centrifugation.

After centrifugation, the plasma layer will be at the top half of the tube. The nucleated cells (WBC) will be in a whitish layer, called the “buffy coat”, just under the plasma and above the red blood cells.

Plasma Preparation:

- Using a transfer pipette take the top two-thirds of the plasma and transfer plasma into a 15 ml conical centrifuge tube, be careful not to disturb the buffy coat layer in the EDTA tube (**NOTE:** see below for buffy coat processing instructions). Centrifuge the 15 ml conical tube at 1200 RPM for 15 minutes at 4°C. If a refrigerated centrifuge is not available, spin sample at room temperature (1200 RPM for 15 minutes). Immediately place the conical tube on wet ice after centrifugation.
- Transfer equal amounts of plasma into two (2) properly labeled polypropylene tubes for cryopreservation being careful not to disturb the small PBMC/pellet.
- Store the two aliquots of plasma samples in the freezer at ≤ -70°C or colder until they are shipped to central lab.

Buffy Coat Preparation:

- From the EDTA tube remove and aliquot the “buffy coat”; be careful not to disturb the layer of red blood cells.
- Store the aliquot of cells in two (2) properly labeled polypropylene tube for cryopreservation.
- Store the sample in the freezer at ≤ -70°C or colder until it is shipped to central lab.

Plasma and buffy coat samples should be batched together and shipped approximately every 4 months. Individual patients should only be included in the shipment if all of their samples have been completed. Samples should be shipped **Monday-Thursday**. Samples must be shipped on dry ice via overnight courier.

14. Administrative

14.1 Protocol Compliance

The study shall be conducted as described in this protocol. All revisions to the protocol must be discussed with, and be prepared by PrECOG and/or representatives. The Investigator should not implement any deviation or change to the protocol or consent without prior review and documented approval from PrECOG and/or representatives and the Institutional Review Board (IRB) of an amendment, except where necessary to eliminate an immediate hazard(s) to study patients.

If a deviation or change to the approved protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB approval, notification will be submitted to the IRB for review and approval as soon as possible afterward. Documentation of approval signed by the chairperson or designee of the IRB(s) should be in the study records. If PrECOG and/or representatives provides an amendment that substantially alters the study design or increases the potential risk to the patient; the consent form must be revised and submitted to the IRB(s) for review and approval; the revised form must be used to obtain consent from patients currently enrolled in the study if they are affected by the Amendment; and the new form must be used to obtain consent from new patients prior to study entry. Information as to who investigators should send correspondence will be provided in additional study documents.

14.2 Institutional Review Board (IRB)

Before study initiation, the Investigator must have written and dated approval from their respective IRB for the protocol, consent form, patient recruitment materials/process and any other written information to be provided to patients. The Investigator should also provide the IRB with a copy of the Investigator Brochure or product labeling, and any updates.

The Investigator should provide the IRB with reports, updates, and other information (e.g., Safety Updates, amendments, and administrative letters) according to regulatory requirements, IRB or study site procedures.

14.3 Informed Consent Procedures

Investigators must ensure that patients who volunteer for clinical trials or their legally acceptable representative are clearly and fully informed about the purpose, potential risks and other information.

A protocol specific informed consent form (ICF) template will be provided to sites. Preparation of the site-specific consent form is the responsibility of the site Investigator and must include all applicable regulatory and IRB requirements, and must adhere to Good Clinical Practices (GCP) and to the ethical principles that have their origin in the Declaration of Helsinki. All changes to the ICF template will be approved by PrECOG and/or their representatives prior to implementation.

In accordance with the Health Information Portability and Accountability Act (HIPAA), the consent process will also include written authorization by patients to release medical information to allow PrECOG and/or its agents, regulatory authorities, and the IRB of record at the study site for access to patient records and medical information relevant to the study, including the medical history. This will be documented in the informed consent form or other approved form obtained at the time of informed consent per institutional policies. This form should also be submitted to PrECOG and/or its agents for review prior to its implementation.

The Investigator must provide the patient or legally acceptable representative with a copy of the consent form and written information about the study in the language in which the patient is most proficient. The language must be non-technical and easily understood. The Investigator should allow time necessary for patient or patient's legally acceptable representative to inquire about the details of the study, then informed consent must be signed and personally dated by the patient or the patient's legally acceptable representative and by the person who conducted

the informed consent discussion. The patient or legally acceptable representative should receive a copy of the signed informed consent and any other written information provided to study patients prior to patient's participation in the trial. The investigator is responsible for assuring adequate documentation of this process and for storage and maintenance of the original signed consent form for each patient/subject.

The informed consent and any other information provided to patients or the patient's legally acceptable representative, should be revised whenever important new information becomes available that is relevant to the patient's consent, and should receive IRB approval prior to use. The Investigator, or a person designated by the Investigator should inform the patient or the patient's legally acceptable representative of all pertinent aspects of the study and of any new information relevant to the patient's willingness to continue participation in the study. This communication should be documented in the patient record. During a patient's participation in the trial, any updates to the consent form and any updates to the written information will be provided to the patient.

14.4 Safety Communication

Investigators will be notified of all AEs that are serious, unexpected, and definitely, probably, or possibly related to the investigational product. Upon receiving such notices, the Investigator must review and retain the notice with the Investigator Brochure and submit a copy of this information to the IRB according to local regulations. The Investigator and IRB will determine if the informed consent requires revision. The Investigator should also comply with the IRB procedures for reporting any other safety information. All revisions should be submitted to PrECOG and/or agents for review.

14.5 Monitoring

Representatives and agents of PrECOG and, as applicable to the study, the manufacturer of investigational product must be allowed to visit all study site locations periodically to assess the data, quality and study integrity. The purpose of this visit is to review study records and directly compare them with source documents and discuss the conduct of the study with the Investigator, and verify that the facilities remain acceptable. Monitoring of drug accountability will also occur.

The study may be evaluated by other auditors and government inspectors who must be allowed access to electronic Case Report Forms (eCRFs), source documents and other study files. The Investigator must notify PrECOG of any scheduled visits by regulatory authorities, and submit copies of all reports. Information as to who investigators should notify of an audit or where to address questions will be provided in additional study materials.

14.6 Study Records

An Investigator is required to maintain adequate regulatory files with corresponding communication and approvals, accurate histories, observations and other data on each individual treated. Full details of required regulatory documents will be provided in additional study materials. Data reported on the eCRFs must be consistent with the source documents as part of the patient record.

The confidentiality of records that could identify patients must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

A study specific signature record will be maintained to document signatures and initials of all persons at a study site who are authorized to make entries and/or corrections on eCRFs as well as document other study-specific roles.

14.7 Electronic Case Report Form (eCRF) Information

Additional information regarding eCRF instructions, timelines for data entry/ submission and query completion can be found in supplemental materials provided to the site. Sites will be expected to complete eCRFs as per the schedule provided and submit all relevant data as per the specified timelines. All items recorded on eCRFs must be found in source documents.

The completed eCRF must be promptly reviewed, electronically signed, and dated by the Principal Investigator.

Instructions for management of patients who do not receive any protocol therapy:

If a patient is registered and does not receive any assigned protocol treatment, baseline, Serious Adverse Event and follow-up data will still be entered and must be submitted according to the eCRF instructions. Document the reason for not starting protocol treatment on the appropriate electronic off treatment form.

14.8 Records Retention

FDA Regulations (21CFR 312.62) require clinical investigators to retain all trial-related documentation, including source documents for the periods described below for studies performed under a US Investigational New Drug (IND):

- two years after the FDA approves the marketing application, or
- two years after the FDA disapproves the application for the indication being studied, or
- two years after the FDA is notified by the sponsor of the discontinuation of trials and that an application will not be submitted.

The Investigator must retain investigational product disposition records, copies of eCRFs (or electronic files), and source documents for the maximum period required by applicable regulations and guidelines, or Institution procedures, whichever is longer. The Investigator must contact PrECOG and/or representatives prior to destroying any records associated with the study.

Information as to who investigators should contact for questions will be provided in additional study documents. PrECOG and/or representatives will notify the Investigator when the trial records for this study are no longer needed.

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Appendix I ECOG Performance Status

PS 0	Fully active, able to carry on all pre-disease performance without restriction
PS 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.
PS 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
PS 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
PS 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

Source: Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair

Appendix II: NYHA Classification

Class	Symptoms
Class I	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath), or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. Comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.
Oxford Textbook of Internal Medicine. Vol. 2, pp 2228. Oxford University Press. 1997	

Appendix III: Ixazomib Medication Diary

Site #:_____	**Subject #:_____**	**Subject Initials:_____**
Cycle:_____	**Dose:_____**	**Number of Capsules: ___ mg: _____**

Patient Instructions:

1. Complete each form as instructed by your physician or study nurse. Please complete in ink.
2. Please complete this diary every day you take ixazomib. Write the date of each dose of ixazomib you take.
3. Ixazomib should be swallowed whole with a glass of water. Capsule should not be opened, broken or chewed. Ixazomib should be taken on an empty stomach (no food or drink) at least 1 hour before or at least 2 hours after food. Each capsule should be swallowed separately with a sip of water. A total of approximately 8 ounces of water should be taken with the capsule.
4. If a dose is not taken at the scheduled time, it can be taken as soon as you remember if the next scheduled dose is 72 hours or more away (beginning with Cycle 2).
5. Extra capsules should not be taken to make up for the missed dose. If you vomit after taking a dose, do not repeat the dose but resume dosing at the time of the next scheduled dose. Please mark dates of any missed capsule on your record.
6. Store your medication refrigerated (36°F to 46°F) for the duration of each cycle.
7. If you have any side effects or comments, please note in the comment section or on the back of the page. If you have questions or concerns, please call _____ at: (_____) _____ - _____.

Please bring your ixazomib blister packs (unused medication and empty blister packs) and this form to every appointment with your study doctor.

DAY	DATE	DOSE	COMMENTS
1	____/____/____	_____mg	
8	____/____/____	_____mg	
15	____/____/____	_____mg	

Appendix IV: Ibrutinib Medication Diary

Site #:_____	**Subject #:_____**	**Subject Initials:_____**
Cycle:_____	**Dose:_____**	**Number of Capsules: 140 mg: _____**

Patient Instructions:

1. Complete each form as instructed by your physician or study nurse. Please complete in ink.
2. Please complete this diary every day. Write the date of each dose of ibrutinib you take.
3. Ibrutinib should be swallowed whole with a glass of water. Capsules should not be opened, broken or chewed. You should take the capsules at approximately the same time each day.
4. If a dose is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day.
5. Extra capsules should not be taken to make up for the missed dose. If you vomit after taking a dose, do not repeat the dose but resume dosing at the time of the next scheduled dose. Please mark dates of any missed capsule on your record.
6. You should not drink grapefruit juice, eat grapefruit, or eat Seville oranges (often used in marmalades) while you are taking ibrutinib. These products may increase the amount of ibrutinib in your blood.
7. Store ibrutinib at room temperature 68°-77°F.
8. If you have any side effects or comments, please note in the comment section or on the back of the page. If you have questions or concerns, please call _____ at: (_____) _____ - _____.

Please bring your ibrutinib bottle(s) (unused medication and empty bottles) and this form to every appointment with your study doctor.

DAY	DATE	DOSE	COMMENTS
1	____/____/____	_____mg	
2	____/____/____	_____mg	
3	____/____/____	_____mg	
4	____/____/____	_____mg	
5	____/____/____	_____mg	
6	____/____/____	_____mg	
7	____/____/____	_____mg	
8	____/____/____	_____mg	
9	____/____/____	_____mg	
10	____/____/____	_____mg	
11	____/____/____	_____mg	

12	____/____/____	_____mg	
13	____/____/____	_____mg	
14	____/____/____	_____mg	
15	____/____/____	_____mg	
16	____/____/____	_____mg	
17	____/____/____	_____mg	
18	____/____/____	_____mg	
19	____/____/____	_____mg	
20	____/____/____	_____mg	
21	____/____/____	_____mg	
22	____/____/____	_____mg	
23	____/____/____	_____mg	
24	____/____/____	_____mg	
25	____/____/____	_____mg	
26	____/____/____	_____mg	
27	____/____/____	_____mg	
28	____/____/____	_____mg	

Appendix V: Investigator's Statement

1. I have carefully read this protocol entitled **"A Phase I/II Study of Ixazomib and Ibrutinib in Patients with Relapsed/Refractory Mantle Cell Lymphoma", Version 3.0 dated 8/21/2020 (Protocol Number PrE0404)** and agree that it contains all the necessary information required to conduct the study. I agree to conduct the study as outlined in the protocol.
2. I agree to conduct this study according to the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, the principles of Good Clinical Practice (GCP) as described in 21 Code of Federal Regulations (CFR) and any applicable local requirements.
3. I understand that this trial and any subsequent changes to the trial will not be initiated without approval of the appropriate Institutional Review Board, and that all administrative requirements of the governing body of the institution will be complied with fully.
4. Informed written consent will be obtained from all participating patients in accordance with institutional and Food and Drug Administration (FDA) requirements as specified in Title 21, CFR, Part 50.
5. I understand that my signature on the electronic Case Report Form (eCRF) indicates that I have carefully reviewed each page and accept full responsibility for the contents thereof.
6. I understand that the information presented in this study protocol is confidential, and I hereby assure that no information based on the conduct of the study will be released without prior consent from PrECOG, LLC unless this requirement is superseded by the FDA.

Principal Investigator (PI):

PI Name: _____

Site Name: _____

Signature of PI: _____

Date of Signature: _______________

MM DD YYYY