PrE0404: Statistical Analysis Plan

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

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LIST OF ABBREVIATIONS

Abbreviation/Acronym	Definition
25(OH)	25-hydroxy vitamin D
AE	Adverse event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
BTK	Bruton's Tyrosine Kinase
CBC	Complete blood count
CR	Complete Response
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-Limiting Toxicity
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylenediaminetetraacetic acid
FFPE	Formalin-Fixed Paraffin-Embedded
FISH	Fluorescence in Situ Hybridization
H&E	Hematoxylin & Eosin
ICH	International Conference on Harmonisation
IV	Intravenous
LDH	Lactate Dehydrogenase
MCL	Mantle Cell Lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
MIPI	Mantle Cell Lymphoma International Prognostic Index
mITT	Modified Intent-to-Treat Population
mL	milliliter
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MTDE	Maximum Tolerated Dose Efficacy Population
ORR	Overall Response Rate
OS	Overall survival
PCR	Polymerase chain reaction

PD	Progressive disease
PET	Positron Emission Tomography
PFS	Progression-free survival
PR	Partial response
QDS	Quality Data Services
RP2D	Recommended Phase II Dose
SAP	Statistical Analysis Plan
SD	Standard deviation OR Stable disease
SPD	Sum of the product of (the two largest perpendicular) diameters
TEAE	Treatment-emergent adverse event
TLF	Tables, listings, and figures
Un	Unevaluable
WBC	White Blood Cells

1. INTRODUCTION

1.1. Objective of the Statistical Analysis Plan

This statistical analysis plan (SAP) describes the planned analysis of the safety and efficacy data from this study. A detailed description of the associated planned tables, listings, and figures (TLFs) to be presented in any reporting of the results of the study, including manuscripts for consideration in academic journals, will be included in the accompanying mock TLFs document.

The intent of this document is to provide guidance for the analysis of safety and efficacy data and to describe any applicable statistical procedures. In general, the analyses come directly from the protocol, unless they have been modified by agreement between PrECOG, LLC and Quality Data Services, Inc. (QDS). A limited amount of information concerning this study (e.g., objectives, study design) is summarized to help the reader interpret the accompanying TLF templates. Attached signatures indicate approval of the statistical analyses sections of the SAP and the accompanying TLF templates. These sections must be agreed upon prior to database lock. When the SAP and TLF templates are agreed upon and finalized, they will serve as the template for generation of the TLFs that will be the basis of the safety and efficacy results described in any reporting of the results of the study.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are different, they will be so identified and a rationale for the change provided. Any substantial deviations from this SAP will be agreed upon between PrECOG, LLC and QDS and documented in an Amendment to the SAP.

2. STUDY OBJECTIVES

2.1. Primary Objectives

- **Phase I**: To determine the maximum tolerated dose (MTD) of ixazomib in combination with ibrutinib in patients with relapsed/refractory mantle cell lymphoma (MCL)
- **Phase II**: To determine the complete response (CR) rate of ixazomib in combination with ibrutinib in relapsed/refractory MCL in ibrutinib-pretreated and ibrutinib-naïve patients

2.2. Secondary Objectives

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

2.3. Exploratory Objectives (Outside of scope of this analysis plan)

- To evaluate the efficacy of the combination in patients previously treated with proteasome inhibitors or ibrutinib
- To evaluate the prognostic importance of high risk cytogenetic alterations in patients with relapsed/refractory MCL receiving ixazomib and ibrutinib
- To evaluate the prognostic significance of vitamin D deficiency in patients with relapsed/refractory MCL
- To assess the frequency and impact of recurrent mutations in patients with relapsed/refractory MCL

2.4. Study Endpoints

2.4.1. Efficacy Endpoints

- Complete Response (CR) rate during phase II
- Overall Response Rate (ORR)
- Overall Survival (OS)
- Progression-Free Survival (PFS)

2.4.2. Safety Endpoints

- Dose-Limiting Toxicities, during Phase I
- Treatment-Related Adverse Event Incidence
- Dose Compliance

3. STUDY DESIGN

3.1. Study Design

3.1.1. Phase I

The phase I portion of the study is a dose finding trial using a standard 3+3 design. The primary objective is to determine the maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) of the combination dose of ixazomib and ibrutinib in adult male and female patients with relapsed or refractory, pathologically proven mantle cell lymphoma (MCL). Both ibrutinib-pretreated and ibrutinib-naïve patients will be enrolled. Patients must not have been exposed to the combination of proteasome inhibitor and Bruton's tyrosine kinase inhibitor, but, if ibrutinib-pretreated, must have discontinued ibrutinib at least 3 months prior to starting study therapy. Planned dose levels are listed in the table below.

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

There will be no dose escalation above Dose Level 2 or dose reduction below Dose Level -1. If dose level 1 is too toxic, the dose will be de-escalated to Level -1. Patients shall continue therapy until progression or unacceptable toxicity.

Patients will 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 an ixazomib dose delay of >72 hours for reasons unrelated to toxicity will not be considered DLTs. These patients will 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. Patients who experience DLTs may also continue on study therapy. Dose Limiting Toxicities for the Phase I study are defined according to the following table:

	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 resolves 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

All patients will complete a PET/CT at the time of study enrollment. Thereafter, restaging will include chest/abdomen/pelvis CT 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 or for patients unable to receive IV contrast dye. Patients who discontinue study therapy for reasons other than disease progression will have CTs performed every 6 months until progression and/or initiation of a new therapy. Tumor response will be assessed by the investigator in accordance with the Lugano criteria.

3.1.2. Phase II

The phase II portion of the study will begin once the MTD/RP2D has been determined from the phase I portion of the study. Adult male and female patients with relapsed or refractory, pathologically proven mantle cell lymphoma (MCL) will be enrolled into two cohorts, based on prior ibrutinib treatment:

ibrutinib-pretreated and ibrutinib-naïve. Any patient who meets the eligibility criteria will be allowed to enroll in the appropriate cohort without any stipulations regarding prior ibrutinib exposure, except that patients must have tolerated prior ibrutinib (i.e., not discontinued therapy due to toxicity) and must not have been exposed to the combination of proteasome inhibitor and BTK inhibitor. Patients will receive therapy at the RP2D, with ibrutinib administered continuously daily and ixazomib administered on days 1, 8, and 15 of a 28-day cycle. Patients will be treated until disease progression or unacceptable toxicity, with dose modifications and delays handled as described in Section 6.5 of the protocol.

All patients will complete a PET/CT at the time of study enrollment. Thereafter, restaging will include chest/abdomen/pelvis CT 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 or for patients unable to receive IV contrast dye. Patients who discontinue study therapy for reasons other than disease progression will have CTs performed every 6 months until progression and/or initiation of a new therapy. Tumor response will be assessed by the investigator in accordance with the Lugano criteria.

3.2. Study Duration

The study will consist of two phases – a Phase I part designed to evaluate safety and tolerability of the dose combination and find the maximum tolerated dose and a Phase II part designed to evaluate the efficacy of the dose combination and further evaluate its safety and tolerability. Both phases will consist of a Screening Period, an indefinite number of 28-day treatment cycles, and Follow-Up. The Follow-Up visit will occur 30 +/- 7 days after last dose of study therapy. If a patient is removed from treatment for reason(s) other than progression, the patient will be followed with regular tumor assessments per standard of care until progression or start of new treatment.

Patients will receive protocol therapy until any one of the following:

- Disease progression per LUGANO criteria or clinical progression
- Toxicities considered unacceptable by either the patient or the investigator, despite optimal supportive care and dose modifications
- Adverse events or treatment delays requiring discontinuation of ixazomib based on dose modification guidelines in Section 6.5.1 of the study protocol
- Development of an inter-current illness that prevents further administration of study treatment
- Extraordinary Medical Circumstances; i.e., the constraints of this protocol becoming detrimental to the patient's health
- Withdrawal of consent or inability to comply with study procedures.

3.3. Study Population

A minimum of 6 and a maximum of 12 patients will be enrolled into the Phase I portion of the study. The exact number will depend upon the number of dose limiting toxicities observed and the dose levels at which those toxicities are observed. For the Phase II portion of the study, 36 patients will be enrolled into each of the two cohorts – ibrutinib-naïve and ibrutinib-pretreated – in effort to obtain 31 eligible, treated patients in each cohort. This will result in a maximum accrual of 84 patients for the full study. Patients who discontinue from the study will not be replaced.

The study population will consist of adult males and females with relapsed or refractory, pathologically proven mantle cell lymphoma (MCL). Patients enrolled into the Phase I portion of the study must not have been exposed to the combination of proteasome inhibitor and Bruton's tyrosine kinase inhibitor, but,

if ibrutinib-pretreated, must have discontinued ibrutinib at least 3 months prior to starting study therapy. For the Phase II portion of the study, anyone enrolling into the ibrutinib-pretreated cohort must have tolerated prior ibrutinib (i.e., not discontinued therapy due to toxicity) and patients enrolling in either Phase II cohort must not have been exposed to any combination of proteasome inhibitor and BTK inhibitor.

3.4. Randomization and Blinding

Randomization will not be used to determine starting treatment level for any patient in either phase of the study. Patients in the Phase I portion of the study will be assigned to one of three set combination dose levels of ibrutinib and ixazomib specified in the protocol. An individual patient's starting dose will be based upon the number of dose-limiting toxicities observed among prior patients in the study. All patients in the Phase II portion of the study, regardless of cohort, will be assigned to the same starting combination dose of ibrutinib and ixazomib determined from the Phase I portion of the study to be the maximum tolerated dose. All doses of ibrutinib and ixazomib will be administered to patients in open-label fashion.

3.5. Treatment Administration

3.5.1. Phase I

Patients will be enrolled to the phase I study through a standard 3 + 3 design. Dose escalation shall occur according to the table below:

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 first three patients will be accrued to Dose Level 1 (3 mg ixazomib and 560 mg ibrutinib). Patients will receive therapy at the maximum tolerated dose from the Phase I portion of the study, with ixazomib administered orally on days 1, 8, and 15 of a 28-day cycle and ibrutinib administered orally daily on all 28 days of each cycle. Patients shall continue therapy until progression or unacceptable toxicity.

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.

Missed doses, regardless of cycle, can always be taken as soon as the patient remembers provided that the next scheduled dose is 72 hours or more away. However, patients on Phase I, Cycle 2 and subsequent cycles will not make up any ixazomib doses that are delayed >72 hours due to toxicity.

For Cycle 1, patients will 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.

Patients who experience a DLT may continue on study therapy. Patients who continue will be subject to dose modifications and/or delays as detailed in sections 6.5.1 and 6.5.2 of the study protocol.

3.5.2. Phase II

Patients will receive therapy at the maximum tolerated dose from the Phase I portion of the study, with ixazomib administered orally on days 1, 8, and 15 of a 28-day cycle and ibrutinib administered orally daily on all 28 days of each cycle. Patients will continue therapy until they have evidence of progression, unacceptable toxicity, or withdrawal of consent.

Missed ixazomib doses may be taken as soon as the patient remembers provided that the next scheduled dose is 72 hours or more away; however, patients will not make up any ixazomib doses that are delayed >72 hours due to toxicity.

For Cycle 1, patients will 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.

Dose modifications and/or delays in response to toxicities or other adverse events of interest will follow the guidelines detailed in sections 6.5.1 and 6.5.2 of the study protocol.

3.6. Study Procedures and Assessments

All study procedures and assessments are listed in the table in **Appendix 1**.

4. GENERAL STATISTICAL CONSIDERATIONS

4.1. Determination of Sample Size

The sample size of the Phase I portion of the study is consistent with the standard 3+3 design. There is one dose level above and one below the starting dose, allowing for only one dose escalation or de-escalation in the study. Thus, a minimum of 6 patients (assuming, for example, ≥2 DLT on each of levels 1 and -1) and a maximum of 12 patients (assuming 6 patients accrued to two dose levels) will be enrolled into the phase I portion of the study.

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 ibrutinib-naïve cohort will be 40%, based on a historical rate of 21% for single agent ibrutinib, and the target CR rate for the ibrutinib-pretreated cohort will be 23% based on a single agent CR rate of 8% for bortezomib. The goal analysis sample for the phase II study is 31 eligible, treated patients in each cohort for a total of 62 eligible, treated patients. This will provide 86% power for the ibrutinib-naïve comparison and 87% power for the ibrutinib-pretreated comparison, allowing for 10% one-sided Type I error and using an exact binomial test in each case. 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.

4.2. Methodology

Phase I data will generally be presented in separate tables, listings, and figures from the Phase II data. Listings will be sorted by cohort (Phase II only), site, patient number, and, if relevant, visit and date and time of assessment. All listings will include flags to indicate patient-level inclusion/exclusion for each of the analysis populations.

Post-dose safety parameters will be summarized by cohort (ibrutinib-naïve vs. ibrutinib-pretreated) for Phase II tables/figures. All tables will use only data pertaining to the specific population being analyzed.

Continuous data will be summarized with the following descriptive statistics: number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical data will be summarized with frequencies of patients and associated percentages based on the number of patients in the given analysis population. Percentages will be computed using the number of patients in the relevant analysis population as the denominator unless stated otherwise.

4.3. Handling of Dropouts or Missing Data

In the Phase I portion of the study, patients experiencing progression prior to Cycle 2, Day 1 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 an ixazomib dose delay of >72 hours for reasons unrelated to toxicity will also 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. All patients replaced for DLT assessments will still be included in safety analyses if at least one dose of ibrutinib or ixazomib was administered. Patients who withdraw from the Phase II portion of the study will not be replaced for any analyses.

If the start date of an adverse event is missing or ambiguous, the event will be assumed to be treatment-emergent, that is, to have started after the first study treatment administration. Similarly, if the relationship of an adverse event to a certain study treatment is not collected, then the adverse event will be assumed to be related to that treatment for inclusion in listings and tables of treatment-related events. The start and end dates of all adverse events and their relationships to study treatments will still be listed as collected.

All other cases of missing or invalid data will be treated as missing and will not be imputed.

4.4. Interim Analyses and Data Monitoring

All statistical analyses and data summaries on Phase I data will be completed immediately following the last Phase I patient's study completion. Analyses on Phase II data will be completed after all Phase II patients exit the study.

PrECOG will convene a data safety monitoring board to review the safety of all enrolled patients and ensure compliance with all appropriate guidelines.

4.5. Multi-center Studies

This study will be conducted at a multiple study sites; however, no statistical adjustments or stratification is deemed necessary for site effects.

4.6. Multiple Comparisons / Multiplicity

No statistical adjustments will be made for multiplicity considerations. The primary objective of the Phase I portion of the study is to determine the MTD of ixazomib in combination with ibrutinib. The MTD will be determined based upon the set rules of the 3+3 study design, not via statistical considerations. The primary objective of the Phase II portion of the study is to compare the observed CR rate to historical single-agent CR rates separately in each of the two cohorts. No adjustment for

multiplicity will be made as the power calculations for the hypothesis tests to evaluate CR rate in each of the two cohorts did not adjust for multiplicity.

4.7. Analysis Populations

This section is designed to identify the characteristics that are necessary for inclusion in particular populations defined for the purpose of analysis. All analyses described in this document will be executed on either the Safety Population, Modified Intent-to-Treat (mITT) Population, or Maximum Tolerated Dose Efficacy (MTDE) Population.

4.7.1. Safety Population

The Safety Population is defined as all patients who received at least one dose of any study treatment – ibrutinib or ixazomib. Phase I patients replaced for the DLT assessment due to protocol non-compliance, progression before the beginning of Cycle 2, or sufficiently long dose delays not caused by a toxicity are still included in the Safety Population if at least one dose of ixazomib or ibrutinib was administered. All summaries and analyses of safety data, including dose compliance and toxicity, will be completed using the Safety Population.

4.7.2. Modified Intent-to-Treat (mITT) Population

The mITT Population will consist of all patients in the Safety Population who met all study eligibility criteria. All non-safety primary and secondary endpoints will be analyzed on the mITT population.

4.7.3. Maximum Tolerated Dose Efficacy (MTDE) Population

The MTDE Population is defined as all patients in the mITT Population from both phases whose starting dose level is the maximum tolerated dose as determined by the Phase I toxicity data. This population will be used for a secondary endpoint analysis of overall response rate (ORR) at the maximum tolerated dose.

5. STUDY POPULATION CHARACTERISTICS

5.1. Patient Accountability and Patient Disposition

The number of patients registered, included in each analysis population, completing the study, and discontinuing treatment will be tabulated by phase, and within Phase II, by cohort and in aggregate (Table 14.1.1). Patients discontinuing treatment will be categorized by reason for discontinuation.

5.2. Demographics and Baseline Characteristics

Demographic data (age, sex, and race) and screening characteristics (ECOG performance status, prior ibrutinib exposure, presence/absence of gastrointestinal involvement and/or splenomegaly, MIPI score and interpretation, and Ann Arbor staging – including presence/absence of B symptoms) will be listed for all patients (Phase I: Listing 16.2.4.1; Phase II: Listing 16.2.4.2). These data, in addition to ethnicity, height, weight, prior fluorescence in-situ hybridization [FISH] testing for t(11;14) and/or del(17p), prior exposure to high dose cytarabine, proteasome inhibitors, and/or radiation therapy, and the nature of any prior bone marrow transplant will be summarized for the Safety Population and the mITT Population (Phase I: Table 14.1.2.1; Phase II: Table 14.1.2.2). The summary for Phase II will be stratified by cohort within analysis population. Descriptive statistics (n, mean, standard deviation, median, minimum, and

maximum for numerical variables, count and percentage for categorical variables) will be presented where applicable.

6. SAFETY ANALYSIS

The post-baseline safety assessments in this study include adverse event assessments and dose compliance. Separate listings will be produced for Phase I data versus Phase II data. All safety data listings will be sorted by cohort (Phase II only), site, and patient number.

All summary statistics for safety data will be subset to the Safety Population.

6.1. Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as events which were not present at baseline or worsened in severity following the patient's first dosing with study treatment. Where the start date of an adverse event is missing or ambiguous, the event will be assumed to be treatment-emergent. Similarly, treatment-emergent adverse events for which the relationship to either of the study treatments was not collected will be assumed to be treatment-related for inclusion in listings and tables of treatment-related adverse events. Nevertheless, the start and end dates of adverse events and their relationships to study treatments will still be listed as collected.

The number of patients who experience TEAEs will be summarized separately by phase. These summaries will also be subdivided in the same table by seriousness, CTCAE v4.0 toxicity grade, outcome, relation to each of the two study medications, and whether or not the event necessitated a dose modification (i.e., a reduction in dose, delay in dosing, or withdrawal of one or both study treatments) or study discontinuation (Phase I: Table 14.3.1.1.1; Phase II: Table 14.3.1.1.2). In the Phase I summary, the number and percent of patients who experienced a dose-limiting toxicity will also be included. The Phase II summary will be stratified by cohort.

Treatment-related AEs with CTCAE v4.0 toxicity grade of three or greater will be summarized by system organ class and preferred term using MedDRA version 21.0 (Phase I: Table 14.3.1.2.1; Phase II: Table 14.3.1.2.2). The Phase II summary will be stratified by cohort. An event will be considered to be treatment-related if it is assessed by the investigator as related, probably related, or possibly related to either of the study treatments. Each table will summarize the number of patients who experience such events, ordering the system organ classes, and preferred terms within each system organ class, by descending incidence rate. A patient will be counted at most once for each preferred term and once for each system organ class, regardless of the number of relevant TEAEs experienced for a given category. The Phase II table will also include a 90% Clopper-Pearson exact two-sided binomial confidence interval for the observed incidence rate of each system organ class and preferred term, and also for the overall total incidence rate across all system organ classes and preferred terms.

Treatment-emergent AEs will be summarized by system organ class and preferred term using MedDRA version 21.0 (Phase I: Table 14.3.1.3.1; Phase II: Table 14.3.1.3.2). The Phase II summary will be stratified by cohort. Both tables will summarize the number of patients who experience such events, ordering the system organ classes, and preferred terms within each system organ class, by descending incidence rate. A patient will be counted at most once for each preferred term and once for each system organ class, regardless of the number of relevant TEAEs experienced for a given category. Statistics will be limited to counts and percentages in both tables; confidence intervals on incidence rates will not be computed.

By-patient listings will present all treatment-emergent AEs (Phase I: Listing 16.2.7.1.1; Phase II: Listing 16.2.7.1.2), and all treatment-related AEs with toxicity grade of three or greater (Phase I: Listing 16.2.7.2.1; Phase II: Listing 16.2.7.2.2). These listings will include MedDRA (version 21.0) system organ class and preferred term, the date of the start and end of each event, the AE duration in days, relationship to and action taken with each of the two study treatments, event outcome, toxicity grade, any criteria met for classification as a serious adverse event, and whether or not the event is a dose-limiting toxicity (Phase I only). A separate listing will present these same details for the set of all dose-limiting toxicities observed in Phase I (Listing 16.2.7.3.1).

6.2. Study Drug Administration and Dose Compliance

Details of study drug administration and dose compliance will be summarized in one table for each phase. The number and percentage of patients who received either study drug will be tabulated by cycle in order to show for each given cycle number how many patients received *at least* that many cycles of treatment. Also, the number of ibrutinib dose reductions and ixazomib dose reductions across all cycles will be summarized by patient counts and percentages. Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be used to summarize the number of scheduled doses missed per cycle for ixazomib and for ibrutinib and the duration in months of patient exposure to study treatment. The Phase I summary will be stratified by starting dose level; that is, level 1, 0, or -1 (Table 14.3.4.1). The Phase II summary will be stratified by cohort (Table 14.3.4.2).

7. EFFICACY ANALYSIS

The efficacy analyses are designed to evaluate separately for each cohort the primary Phase II endpoint of CR rate according to the Lugano criteria and also to evaluate the secondary endpoints of overall response rate, overall survival, and time to disease progression in each phase of the study. All efficacy endpoints are evaluated on the Modified Intent-to-Treat (mITT) Population; however, the secondary endpoint of overall response rate is also evaluated on the Maximum Tolerated Dose Efficacy (MTDE) Population, which combines mITT patients from both phases but subsets the Phase I patients to only those whose starting dose was the maximum tolerated dose as determined by the Phase I toxicity data.

7.1. Primary and Secondary Efficacy Endpoint Analyses

The **primary endpoint** in the Phase II portion of the study is the complete response (CR) rate in ibrutinib-naïve and ibrutinib-pretreated patients within the first 12 months of study treatment. This proportion will be computed by cohort for the Phase II patients in the mITT Population and presented along with the Clopper-Pearson exact 1-sided 90% confidence bound of the proportion, expressed as a percent (Table 14.2.1). The same table will show the proportion of Phase II patients in the mITT Population whose best overall disease response during the 12 months after starting treatment with ixazomib and ibrutinib is a complete response (CR), a partial response (PR), stable disease (SD), progressive disease (PD), and unevaluable (Un). The disease response option of 'unevaluable (Un)' is not a collected value on the CRF but will be used in analysis for patients who do not have a valid disease response assessment during the given period for any reason, including termination of study treatment prior to a patient's first on-treatment disease response assessment.

The historical single-agent CR rate for ibrutinib in relapsed/refractory MCL is 21%, thus the combination therapy will be considered to show evidence of superiority to ibrutinib monotherapy in ibrutinib-naïve patients if the lower bound of a 1-sided 90% Clopper-Pearson exact confidence interval is > 21% in the ibrutinib-naïve cohort (Cohort A). The implied hypothesis test is designed to have 86% power if there are

31 patients in the ibrutinib-naïve cohort of Phase II, given an alternative hypothesis of a CR rate of 40% for the combination therapy.

The single agent CR rate for bortezomib was previously reported as 8%, thus the combination therapy will be considered to show evidence of superiority to a combination therapy of ibrutinib and bortezomib in ibrutinib-pretreated patients if the lower bound of a 1-sided 90% Clopper-Pearson exact confidence interval is > 8% in the ibrutinib-pretreated cohort (Cohort B). The implied hypothesis test is designed to have 87% power if there are 31 patients in the ibrutinib-pretreated cohort of Phase II, given an alternative hypothesis of a CR rate of 23% for the combination therapy of ixazomib and ibrutinib.

One of the **secondary endpoints** of both study phases is the Overall Response Rate across all post-baseline disease response assessments. Overall Response Rate is defined as the proportion of patients who achieved a partial response (PR) or complete response (CR) at any disease response assessment over the course of the study. The Overall Response Rate will be computed separately for each phase of the mITT Population (Phase I: Table 14.2.2.1; Phase II: Table 14.2.2.2). The Phase II analysis will be stratified by cohort and will present a two-sided 90% Clopper-Pearson exact confidence interval of the Overall Response Rate expressed as a percent. Both the Phase I and Phase II tables will also present the best overall disease response, i.e., CR, PR, SD, PD or Un, across all post-baseline study assessments and a summary of the duration of the response in months among the patients who attained a PR or CR at any time post-baseline. The response duration will be modeled using the Kaplan-Meier product-limit method for each phase. Response duration is defined as time from the documentation of best response of CR or PR until disease progression or death. Patients alive and without progression will be censored at the date of last disease assessment. The number and percent of patients in the mITT Population who died or whose disease progressed on study and the number of patients censored will be summarized along with the Kaplan-Meier median response duration times and corresponding 90% confidence intervals. The 90% confidence intervals will be computed using Greenwood's formula.

Overall Response Rate will also be assessed on the Maximum Tolerated Dose Efficacy (MTDE) Population; that is, the set of all eligible, treated patients in either study phase whose starting dose is the maximum tolerated dose as determined from the Phase I toxicity data (Table 14.2.2.3). The table will be stratified by prior ibrutinib status – i.e., ibrutinib-naïve versus ibrutinib-pretreated – and will present a two-sided 90% Clopper-Pearson exact confidence interval of the Overall Response Rate expressed as a percent. A summary of best disease response across all post-baseline study assessments and Kaplan-Meier product-limit estimates of median response duration will be included in the same table.

Patient-level response duration will be shown graphically by cohort for Phase II patients in the mITT Population via swimmer plots (Figure 14.2.7). Each plot will have one horizontal bar per patient showing treatment duration in months. Notations will be included for start and end of response.

The **secondary endpoints** of progression-free survival (PFS) and overall survival (OS) will be modeled using the Kaplan-Meier product-limit method for each study phase. Progression-free survival represents the time from the patient's enrollment in the study until either death or disease progression, whichever occurs first. Censoring for progression-free survival occurs at the date that disease response was last adequately assessed as a part of study procedures. Overall survival represents the time from the patient's enrollment in the study until death from any cause. Censoring for overall survival occurs at the date of last contact with the patient as a part of on-treatment procedures or follow-up assessments. The Kaplan-Meier survival curves for progression-free survival and overall survival will be presented for the mITT Population in Figures 14.2.5.1 and 14.2.6.1, respectively, for Phase I patients, and in Figures 14.2.5.2 and 14.2.6.2, respectively, for Phase II patients. The number of patients remaining in the risk set at each 3-

month timepoint and the number of patients censored at the beginning/end of each 3-month interval will be listed below each figure. The Kaplan-Meier median survival times and corresponding 90% confidence intervals will also be provided for each survival curve. The 90% confidence intervals will be computed using Greenwood's formula. The Phase II figures will include a separate survival curve and separate median estimates and risk set and censoring subject counts for each cohort.

The assessment results for disease response (Phase I: Listing 16.2.6.1.1; Phase II: Listing 16.2.6.1.2) and target lesion size (Phase I: Listing 16.2.6.2.1; Phase II: Listing 16.2.6.2.2) will be listed by cohort (Phase II only), site, patient, visit, time point, and date of assessment. The listing of target lesion assessments will have one row per target lesion and will indicate the length of the tumor in its two longest perpendicular dimensions and also the product of these two perpendicular measurements.

The target lesion, non-target lesion, and overall disease responses (CR, PR, SD, PD, or Unevaluable) will be summarized on the mITT Population for each assessment along with the best target, non-target, and overall response observed across all post-baseline study assessments (Phase I: Table 14.2.3.1; Phase II: Table 14.2.3.2). The Phase II table will be stratified by cohort. The best target lesion response will also be shown graphically (Phase I: Figure 14.2.4.1; Phase II: Figure 14.2.4.2). The figure represents each patient's maximum percent decrease in the sum over all target lesions of the product of each lesion's two largest perpendicular diameters (SPD) as a vertical bar in a waterfall plot. The bars will be colored according to the patient's best overall disease response over both treatment phases. Three colors will be used to distinguish complete responses (CR) from partial responses (PR) and stable or progressive disease (SD/PD). The Phase II figure will include two plots – one per cohort.

8. SUMMARY OF CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

There are no changes to the planned primary and secondary endpoint analyses described in version 1.0 of the clinical trial protocol dated September 20, 2017.

9. REPORTING CONVENTIONS

The mean and median will be displayed to one decimal place greater than the original value, and the standard deviation will be displayed to two decimal places greater than the original value. All statistical programming and analyses will be performed using SAS® Release 9.2 or later (SAS Institute Inc., Cary, North Carolina, USA).

The following standards will be used in the data presentation:

- The filenames for each individual listing, table, or figure will include both the unique number assigned to the particular listing, table, or figure in the accompanying mock TLF document and a brief description of the contents of the output (i.e., a shortened form of the title).

- Percentages presented in in-text tables should be rounded to one decimal using the SAS rounding function. If "%" is part of the column heading, do not repeat the "%" sign in the body of the table. Unless specified otherwise, "%" should reflect the total population of the treatment group/cohort. Any deviation from that should be part of the footnote. For 0 counts, the corresponding percentage should be left blank, as should 0/0.

- SD should be the default for representing scale, unless standard error has been specified. Standard deviation should be abbreviated as "SD", and presented below the mean value. The SD should have

one additional decimal place beyond that of the mean (e.g., mean has one decimal place, SD should have two).

- If the table or listing is too long to display on one page, the additional (treatment group/cohort) columns will be continued on the following pages.

- "N" will represent the entire treatment group/cohort for the population and phase(s) being analyzed, while "n" will represent a subset of "N". For tables with population designated as a row heading, "N" should be used (i.e., tables where all participant data is not available for every variable within a treatment/memory status group). As a guideline, if the number is used in a denominator, it should be presented as "N". If the number is used in the numerator, it should be presented as an "n".

- The heading should consist of four lines. Line 1: Sponsor identifier. Line 2: Protocol identifier. Line 3: blank line. Line 4: Table/Appendix number Table Title – Population. The title for in-text tables should begin with the Table/Appendix number. The footer will include a line noting whether the table, listing, or figure is draft or final and blinded or unblinded (i.e., 'Unblinded Draft', 'Blinded Final', etc.).

- All data listings will be sorted by cohort (Phase II only), site, patient number, visit, and date/time (as applicable).

- The date format for all dates is DDMMMYYYY.

- If no data are collected for use in the tables and listings, then a table and/or listing will be created stating that no data are available.

- A solid line should appear both above and below the column headings of a table. A solid line should appear at the end of the table or at the bottom of each page if the table extends to more than one page. Footnotes should start after the bottom solid line.

10. REFERENCES

1. SAS Institute, Inc., SAS® Version 9.2 software, Cary, NC.

2. ICH Guidance for Industry: E9 Statistical Principles for Clinical Trials, 1998.

3. ICH Guidance for Industry: E3 Structure and Contents for Clinical Study Report, 1996.

APPENDIX 1. STUDY PROCEDURES AND ASSESSMENTS

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 and Subsequent Cycles*				Every 3 Cycles*	Off Treatment[13]	Follow-Up[15]
		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			
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					X	
Vital Signs (Temperature, Pulse, Blood Pressure)	X	X	X	X		X					X	
Performance Status	X	X				X					X	
CBC/Differential/Platelets[2]	X	X	X	X	X	X		X[2]			X	
Chemistry[3]	X	X	X	X		X					X	
PT/INR	X											
Lactate Dehydrogenase (LDH)	X											
Vitamin D Level[4]	X											
Peripheral Blood Flow Cytometry	X											

Procedures	Screening	Cycle 1* (1 cycle=28 Days)				Cycle 2 and Subsequent Cycles*				Every 3 Cycles*	Off Treatment[13]	Follow-Up[15]
		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			
Serum Pregnancy Test[5]	X											
PET/CT	X											
Chest/Abdomen/Pelvic MRI or CT with Contrast[6]										X[12]	X	
Bone Marrow Aspirate and Biopsy[7]	X										X[7]	
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	X		X						
Concomitant Medication Review	X	X	X	X		X					X	
Adverse Events Assessment		X	X	X		X					X[14]	
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 prior to each dose of chemotherapy.

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 II: Days 1, 8 and 15 of Cycle 1, then Day 1 of subsequent cycles.

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.

   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, but if this occurs, the CT portion must include IV contrast unless otherwise contraindicated due to allergy or impaired renal function.
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.

    <u>Screening/Study Entry</u>
    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

    <u>After Cycle 3 (+/- 5 days of Cycle 4, Day 1)</u>
    Peripheral Blood: Two 6 mL in EDTA tubes

    <u>At time of Suspected CR</u>
    Peripheral Blood: Two 6 mL in EDTA tubes

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

    NOTE: 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 during Cycle 1. 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 of protocol). Ibrutinib shall be administered orally daily on days 1-28 [Section 6.1.2 of protocol for dosing administration]. Ibrutinib Medication Diary will be reviewed for compliance and collected every cycle (Appendix IV of protocol). See Section 6.2 of protocol for Phase I and Section 6.3 for Phase II dosing instructions and Section 6.5 for dose delays/modifications.

12. 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.**
13. 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.
14. 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.
15. 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.

DOCUMENT HISTORY

Version Date	Modified By	Summary of Changes