PrE0405: Statistical Analysis Plan

Phase II Study of Bendamustine and Rituximab plus Venetoclax in Untreated Mantle Cell Lymphoma over 60 Years of Age

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Statistical Analysis Plan

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Phase II Study of Bendamustine and Rituximab plus Venetoclax in Untreated Mantle Cell Lymphoma over 60 Years of Age

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation/Acronym	Definition
AE	Adverse event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
BR	Bendamustine + Rituximab
BSA	Body surface area
BUN	Blood Urea Nitrogen
CBC	Complete blood count
cm	Centimeters
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylenediamine Tetraacetic Acid
FFPE	Formalin-Fixed Paraffin-Embedded
GCSF	Granulocyte Colony-Stimulating Factor
H&E	Hematoxylin & Eosin
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
Hct	Hematocrit
HCV	Hepatitis C virus
Hgb	Hemoglobin
IRB	Investigational Review Board
IV	Intravenous
mcg	microgram
MCL	Mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mg/m^2	Milligrams per square meter of body surface area
MIPI	MCL International Prognostic Index

mITT	Modified Intent-to-Treat Population
mL	milliliter
MRD	Minimum Residual Disease
OBI	On-Body Injector
ORR	Overall Response Rate
OS	Overall survival
PCR	Polymerase chain reaction
PD	Progressive disease
PET	Positron Emission Tomography
PFS	Progression-free survival
PO	*Per os*; By mouth (orally)
PR	Partial response
QDS	Quality Data Services
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard deviation OR Stable disease
SPD	Sum of the product of (the two largest perpendicular) diameters
SQ	Subcutaneous
TEAE	Treatment-emergent adverse event
TLFs	Tables, listings, and figures
TLS	Tumor lysis syndrome
Un	Unevaluable
WBC	White Blood Cells

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 analysis 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 Objective

- To determine the CR rate of BR + venetoclax in untreated MCL patients over the age of 60 years

2.2. Secondary Objectives

- To evaluate the safety of the combination, with particular attention to TLS incidence with Cycle 1
- To determine the overall response rate (complete response [CR] + partial response [PR]) of BR + venetoclax in untreated MCL patients over the age of 60 years
- To determine the survival (progression-free survival [PFS] and overall survival [OS]) of MCL patients treated with BR + venetoclax induction

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

- To evaluate the bone marrow aspirate and peripheral blood assessed minimal residual disease (MRD) negative rate of BR + venetoclax in untreated MCL patients over the age of 60 years
- To evaluate the utility of morphologic assessment of bone marrow biopsy and aspiration when combined with peripheral blood MRD and PET assessments on CR rate at end of treatment

2.4. Study Endpoints

2.4.1. Efficacy Endpoints

- Incidence of complete response (CR) by the end of induction
- Overall response rate (complete response [CR] + partial response [PR]), through the end of induction
- Overall response rate (complete response [CR] + partial response [PR]), through the end of treatment (including both induction and, where relevant, maintenance)
- Progression-free survival (PFS)
- Overall survival (OS)
- Duration of response (either partial or complete)

2.4.2. Safety Endpoints

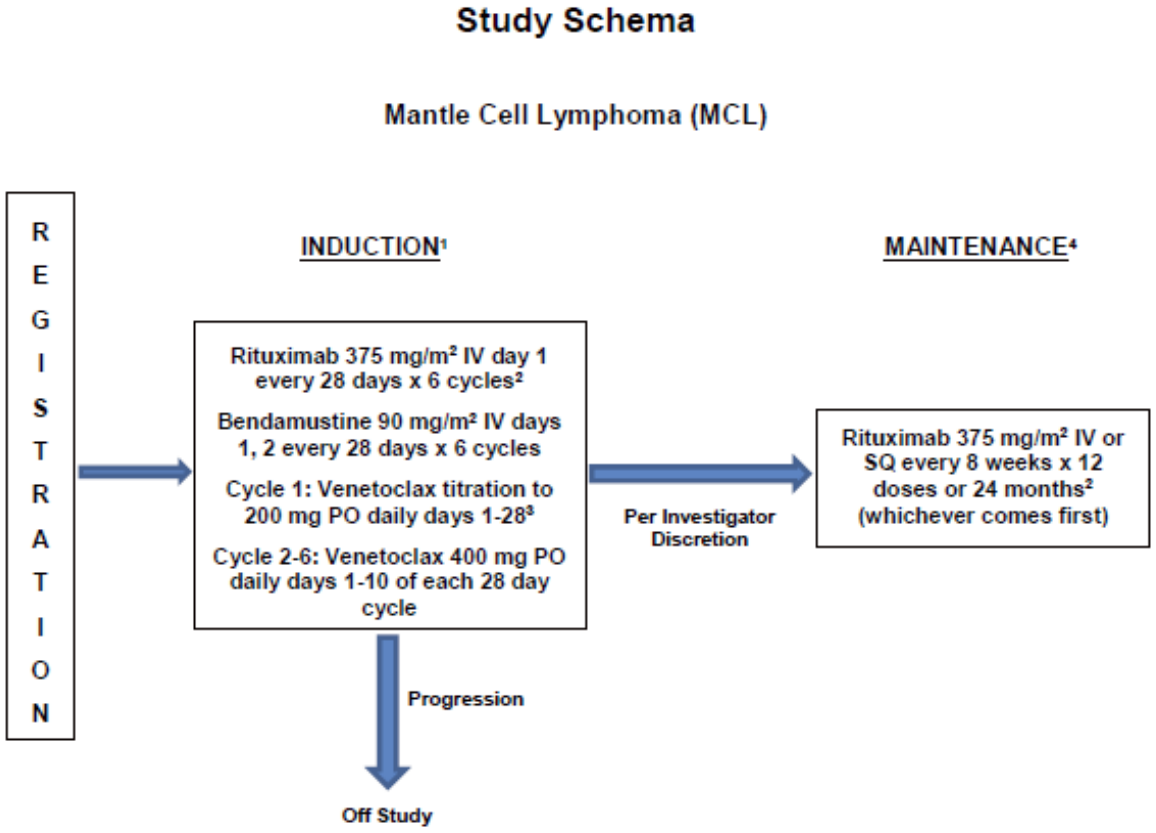
- Adverse events, including
    - Incidence rate of treatment-related events of CTCAE grade 3 or higher
    - Incidence rate of tumor lysis syndrome
    - Incidence rate of non-disease-related death events
    - Incidence rate of serious adverse events (SAEs)
- Exposure to study treatments

3. STUDY DESIGN

3.1. Study Design

This is a single-arm phase II clinical trial in treatment-naïve adult male and female subjects over 60 years of age with a histologically confirmed (biopsy-proven) diagnosis of mantle cell lymphoma (MCL) and measurable or evaluable disease as defined as a lymph node measuring >1.5 cm in any dimension or splenomegaly with spleen >15 cm in craniocaudal dimension. Eligible patients will receive venetoclax, bendamustine, and rituximab as induction therapy for 6 cycles of 28 ± 3 days in length. Upon completing six cycles of induction therapy, subjects may be administered maintenance rituximab per physician discretion. The recommended schedule for maintenance rituximab is every 8 ± 2 weeks for 12 doses or 24 months (whichever comes first). More details on the treatment schedule can be found in the following schema:

Figure 1 Study Schema



Accrual goal: 56 patients

Cycle length: 28 days (4 weeks)

[1] Interim safety analysis planned after 19 patients are enrolled for review of tumor lysis syndrome (TLS) events. Section 12.2.1 for details.

[2] If the first two cycles of intravenous (IV) rituximab are well tolerated, IV rituximab may be replaced with 1400 mg/23,400 units subcutaneous (SQ) rituximab/hyaluronic acid on Day 1 of Cycles 3-6. See Section 5.2.3 for details.

[3] Cycle 1: Goal venetoclax dose will be 400 mg but careful titration and escalation of dose will need to be done during Cycle 1 to mitigate the risk of TLS. See Section 5.3 and Section 5.4 for details.

[4] After 6 cycles of venetoclax, bendamustine and rituximab, subjects responding to therapy may receive maintenance rituximab (one dose every 8 ± 2 weeks for 12 doses or 24 months whichever comes first) per physician and patient preference.

NOTE: At the time of restaging (or if a scan is done earlier for another reason) and disease progression is noted, patients will come off study.

Tumor assessments will be performed in the form of CT or PET/CT before Cycle 3 or 4 and PET/CT after Cycle 6 (6-8 weeks after Cycle 6 Day 1). After the PET/CT at the end of induction, all other imaging will be per institution standards. Subjects will be followed until progression or for up to 5 years from induction treatment discontinuation or study closure. Response and progression will be evaluated using the international criteria proposed by the 11th International Conference on Malignant Lymphoma in Lugano Switzerland (Lugano Classification).

3.2. Study Duration

The study will consist of 2 periods: an Induction Treatment Period (6 cycles of 28 days each), followed by a Follow-up Period (5 years from induction treatment discontinuation or study closure) during which to monitor survival status, disease progression, and initiation of new cancer therapies. Maintenance therapy (maximum of 24 months) may be administered during the Follow-up Period according to investigator discretion. The total duration of the study for each subject will be a maximum of 5.5 years.

Subjects will receive study therapy until disease progression, unacceptable toxicity, development of an inter-current illness that prohibits continuation of treatment, voluntary withdrawal of subject consent, inability to comply with study procedures, investigator determination that protocol requirements are detrimental to subject health, or completion of 6 cycles of induction treatment (and 12 doses or 24 months of maintenance rituximab, if recommended by the investigator).

3.3. Study Population

A total of 56 subjects will be enrolled, 53 of whom are expected to be eligible and treated. Subjects who discontinue from the study will not be replaced.

The study population will consist of treatment-naïve adult male and female subjects over 60 years of age with a histologically confirmed (biopsy-proven) diagnosis of mantle cell lymphoma (MCL) and measurable or evaluable disease as defined as a lymph node measuring >1.5 cm in any dimension or splenomegaly with spleen >15 cm in craniocaudal dimension.

3.4. Randomization and Blinding

All subjects will follow the same open-label treatment regimen.

3.5. Treatment Administration

Eligible subjects will be treated in a single arm with venetoclax, bendamustine, and rituximab as induction therapy for 6 cycles of 28 ± 3 days in length as outlined in the table below:

Agent	Route	Dose	Days
Venetoclax	Oral	20 mg 50 mg 100 mg 200 mg 400 mg	Day 1-7 (Cycle 1 only) Day 8-14 (Cycle 1 only) Day 15-21 (Cycle 1 only) Day 22-28 (Cycle 1 only) Day 1-10 (Cycle 2-6)
Bendamustine	IV	90 mg/m^2	Day 1 and 2 (Cycle 1-6)
Rituximab[a]	IV SQ (optional)	375 mg/m^2 1400 mg (optional)	Day 1 (Cycle 1-6[a]) Day 1 (Cycle 3-6) (optional)

[a] Rituximab should be administered as 375 mg/m^2 IV on day 1 of each cycle. If the first two cycles of rituximab are well-tolerated, IV rituximab may be replaced with 1400 mg/23,400 units subcutaneous (SQ) rituximab/hyaluronic acid on Day 1 of Cycles 3-6, per rituximab/hyaluronic acid package insert.

Due to risk of tumor lysis syndrome, the daily dose of venetoclax is titrated from 20 mg to 200 mg by the end of cycle 1. Venetoclax is then dosed at 400 mg per day, days 1-10 only, for each of the remaining 5 cycles of induction. Dose compliance for venetoclax will be monitored via pill counts and an IRB reviewed medication diary.

Upon completion of 6 cycles of induction therapy, maintenance rituximab may be administered per physician discretion to subjects responding to therapy. The recommended schedule for maintenance rituximab is every 8 ± 2 weeks for 12 doses or 24 months (whichever comes first). The maintenance administration may be either the 375 mg/m^2 intravenous dose or the 1400 mg/23,400 unit subcutaneous dose of rituximab/hyaluronic acid in accordance with physician and patient preference.

If toxicities occur during cycle 1, the Venetoclax dose will be held until resolution and then rechallenge will occur at the same dose. If tumor lysis syndrome is suspected during cycle 1, venetoclax will be held until resolution and then restarted at same dose level if the subject was taking 20 mg daily and one titration dose level lower otherwise (i.e., at 20 mg, 50 mg, or 100 mg if the subject was receiving 50 mg, 100 mg, or 200 mg daily, respectively).

Dose reductions resulting from on-treatment toxicities during induction cycles 2-6 will follow the table below:

Dose Level	**Venetoclax**	**Bendamustine**	**Rituximab**
0 (starting dose)	400 mg PO daily x 10 days	90 mg/m^2 IV days 1 and 2	No dose modifications
-1 (first reduction)	400 mg PO daily x 5 days	90 mg/m^2 IV days 1 and 2	No dose modifications
-2 (second reduction)	400 mg PO daily x 5 days	70 mg/m^2 IV days 1 and 2	No dose modifications

Toxicities warranting a dose reduction while the subject is being dosed at level -2 will result in the subject being discontinued from all study treatments. If tumor lysis syndrome is suspected during cycles 2-6, venetoclax will be held for the rest of the cycle and upon resolution will be restarted at the same dose level at the start of the next cycle.

Acetaminophen and diphenhydramine (or another anti-histamine) will be administered prior to each infusion or injection of rituximab, per institution guidelines. Standard anti-emetic therapy may be given to patients prior to administration of bendamustine per institutional guidelines. However, 5-HT3 serotonin receptor agonist and steroids are strongly recommended.

To mitigate the risk of neutropenic sepsis and febrile neutropenia due to bendamustine or venetoclax, prophylaxis will be required for all subjects with one of the following growth colony stimulating factors (GCSFs) to be administered 24-72 hours after the last dose of bendamustine for each cycle:

- Pegfilgrastim SQ 6 mcg once
- Pegfilgrastim SQ 6 mcg via on-body injector (OBI) once
- Filgrastim or filgrastim-sndz SQ 300 or 480 mcg for 5 days

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 primary endpoint of this single arm Phase II study is CR rate after 6 cycles of BR + venetoclax. A 15% improvement in the historical post-induction CR rate of 70% to 85% is of interest. A total of 56 subjects will be enrolled, 53 of whom are expected to be eligible and treated. In order to have 90% power to detect the 15% improvement in CR rate from 70% using a one-sided exact binomial test with 10% Type I error, 53 subjects will be needed for the analysis. A total of 56 subjects will be enrolled with the expectation that 53 will be eligible and treated.

4.2. Methodology

In general, listings will be sorted by site, subject number, visit, and date and time of assessment or event. All listings will include flags to indicate subject-level inclusion/exclusion for each of the analysis populations.

Post-dose safety and efficacy parameters will be summarized for all subjects in aggregate. 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 subjects and associated percentages based on the number of subjects in the given analysis population.

4.3. Handling of Dropouts or Missing Data

Subjects who withdraw from the study will not be replaced.

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

A review of tumor lysis syndrome (TLS) events will be conducted at interim once 19 subjects (> 1/3 of enrollment goal) have been enrolled in the study and either completed cycle 1 of induction treatment or discontinued treatment. A TLS incidence rate of no more than 15% (≤ 3 out of 19 subjects) is permissible on this study. If the observed TLS incidence rate is ≥ 21% (≥ 4 out of 19 subjects) then a detailed review of TLS cases will be conducted by the Data Safety Monitoring Board (DSMB) to decide whether to recommend closing the study due to unacceptable TLS risk. If the true incidence rate of TLS is 30% or higher, there is at least 87% probability of crossing the boundary; whereas, if the true incidence of TLS is 10%, there is only 11% chance of crossing the boundary.

4.5. Multi-center Studies

This study will be conducted at 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. This study has a single primary objective which is evaluated via a single confidence interval. TLS incidence rate will be evaluated for a decision rule at interim at 1/3 of the accrual goal; however, TLS incidence will not be evaluated at the end of the study via a decision rule or hypothesis test. Thus, there are no multiplicity considerations related to the interim analysis.

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

4.7.1. Safety Population

The Safety Population is defined as all subjects who received at least one dose of any study treatment – bendamustine, rituximab, or venetoclax. All summaries and analyses of safety data, including treatment exposure and toxicity, will be completed on the Safety Population.

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

The mITT Population will consist of all subjects in the Safety Population who met all study eligibility criteria. All efficacy endpoints (primary and secondary) will be evaluated on the mITT population.

5. STUDY POPULATION CHARACTERISTICS

5.1. Subject Accountability and Subject Disposition

The number of subjects registered, included in each analysis population, continuing to maintenance therapy, and completing the study versus discontinuing the study will be tabulated (Table 14.1.1). Subjects discontinuing treatment will be categorized by reason for discontinuation separately for each treatment phase (induction versus maintenance). All treated subjects also will be tabulated by site.

5.2. Demographics and Baseline Characteristics

Demographic data (age, sex, race, and ethnicity) and screening characteristics (weight; spleen size; MIPI score; ECOG performance status; tumor, lymph node, and metastasis staging; and Ann Arbor staging – including presence/absence of B symptoms) will be summarized for the Safety Population and mITT Population (Table 14.1.2). Descriptive statistics (mean, standard deviation, median, minimum, and maximum for numeric variables, count and percentage for categorical variables) will be presented as applicable.

6. SAFETY ANALYSIS

The post-baseline safety assessments in this study include adverse event assessments and study treatment exposure. All safety data listings will be sorted by site and subject 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 subject'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 any one of the study treatments was not collected will be assumed to be treatment-related for inclusion in 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 subjects who experience TEAEs will be summarized. This count of subjects experiencing TEAEs will be subdivided in the same table by seriousness, CTCAE v5.0 toxicity grade, outcome, relation to each of the three study medications, whether the event necessitated a dose modification (i.e., a reduction in dose, delay or interruption in dosing, or withdrawal of one or more study treatments), whether the event resulted in study discontinuation, and various combinations of these criteria. To support the safety endpoints of tumor lysis syndrome and non-disease-related deaths during induction, the number of subjects experiencing these events will also be tabulated with tumor lysis syndrome events subdivided between events during induction cycle 1 and those after cycle 1 (Table 14.3.1.1). The set of all non-disease-related death events during induction also will be listed by subject (Listing 16.2.7). The listing will include the MedDRA (version 22.0) system organ class and preferred term, the date and time and study day relative to the first study treatment administration of the start and end of the event, the AE duration in days, relationship to and action taken with each of the three study treatments, event outcome, and all criteria met for classification as a serious adverse event. Study day will be calculated for the listing as (adverse event start/end date – first study treatment dosing date + 1) since all events in the listing will start and end on or after the first day of induction treatment.

Treatment-related AEs with CTCAE v5.0 toxicity grade of three or greater will be summarized by system organ class and preferred term using MedDRA version 22.0 (Table 14.3.1.2). An event will be considered to be treatment-related if its relationship to any of the three study treatments is assessed by the investigator as definite, probable, or possible. The table will summarize the number of subjects who experience such events, ordering the system organ classes, and preferred terms within each system organ class, by descending incidence rate. A subject 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 table will also include a 90% Clopper-Pearson exact 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.

A separate table will count by system organ class and preferred term subjects who experience treatment-emergent SAEs, regardless of relationship to the study treatments (Table 14.3.1.3). This table, too, will order the system organ classes, and preferred terms within each system organ class, by descending incidence rate.

6.2. Study Drug Administration and Dose Compliance

The number of cycles in which any of the three study treatments were administered will be tabulated separately for induction and maintenance by counts of subjects and associated percentages (Table 14.3.5). The number of subjects who experienced dose reductions will also be summarized by treatment (i.e., bendamustine anytime during induction, venetoclax during titration [cycle 1], and venetoclax during cycles 2-6) with counts and percentages based on the number of subjects who received at least one dose of the given treatment during the given cycle(s). The reasons for dose reductions in bendamustine and any cycle of venetoclax will be summarized similarly by counts and percentages. To describe the actual exposure to bendamustine, considering dose reductions and any non-compliance, the mean dose per administration will be summarized with descriptive statistics (n, mean, standard deviation, median, minimum, maximum). The actual venetoclax exposure will be summarized as dose intensity per 6 weeks for induction cycle 1 and separately for cycles 2-6. Dose intensity is defined as [cumulative dose / treatment duration], normalized to a six-week treatment duration. Since the cumulative venetoclax exposure during cycle 1 will depend on whether toxicities occur that delay the titration schedule, the cycle 1 venetoclax exposure will be summarized also via descriptive statistics of the number of days of venetoclax dosing during cycle 1. As the rituximab dose is dependent on the formulation (IV vs. SQ), with the subcutaneous dose expected to be delivered in full at all relevant administrations, the exposure to rituximab during induction and during maintenance each will be summarized with descriptive statistics of the mean rituximab dose per IV administration. Also to be summarized with descriptive statistics is the duration of rituximab maintenance therapy in months.

7. EFFICACY ANALYSIS

The efficacy analyses are designed to evaluate the CR rate according to the Lugano criteria through the end of induction treatment, the overall response rate (complete response [CR] or partial response [PR]) through the end of induction treatment and through the end of all study treatment, including maintenance, where relevant, and survival and progression-free survival through the end of the five-year follow-up period after induction. All efficacy endpoints are evaluated on the Modified Intent-to-Treat (mITT) Population.

7.1. Primary and Secondary Efficacy Endpoint Analyses

The **primary endpoint** in this study is the proportion of eligible and treated subjects who achieve a complete response (CR) at any disease response assessment through the end of induction treatment. This proportion will be computed for the mITT Population and presented along with the Clopper-Pearson exact 90% lower confidence bound on the proportion, expressed as a percent (Table 14.2.1). The treatment combination of BR + venetoclax will be considered worthy of further investigation if the one-sided 90% lower confidence bound is greater than 70%. For the desired size of 53 subjects for the mITT Population, this equates to 42 or more subjects achieving CR. The hypothesis test implied by the lower confidence bound and defined formally as H_0: CR rate = 70%, H_A: CR rate > 70% has 90% power assuming a true CR rate of 85%.

The same table (Table 14.2.1) will show the proportion of subjects in the mITT Population whose best overall disease response during induction treatment was a partial response (PR), stable disease (SD), progressive disease (PD), or unevaluable (Un). The disease response option of ‘unevaluable (Un)’ is not a collected value on the CRF, but will be used in analysis for subjects who do not have a valid disease response assessment during induction for any reason, including termination of study treatment prior to a subject’s first on-treatment disease response assessment during induction. The table also will display the

overall response rate (ORR) through the end of induction treatment and summarize subjects' Deauville scores from the assessment at the end of induction with counts and percentages for each potential score. The overall response rate is defined as the proportion of subjects whose best overall disease response was either a complete response (CR) or a partial response (PR).

One of the **secondary endpoints** of the study is the Overall Response Rate across both induction and maintenance treatment phases. The Overall Response Rate will be computed for the mITT Population and the count of subjects with a response will be subdivided by the time of eventual death or disease progression – during induction, during maintenance therapy, during the post-treatment follow-up period, or absence of such an event prior to study discontinuation (Table 14.2.2). The table will also summarize the best overall disease response, i.e., CR, PR, SD, PD, or Un, across all induction and maintenance assessments and present the Kaplan-Meier estimate of the median duration in months of overall response among subjects who attained a PR or CR during either induction or maintenance therapy. A 90% confidence interval of the median response duration estimate will be computed using Brookmeyer and Crowley's method[1] and presented.

The **secondary endpoints** of progression-free survival (PFS) and overall survival (OS) will be modeled using the Kaplan-Meier product-limit method. Progression-free survival represents the time from the subject'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 subject's enrollment in the study until death from any cause. Censoring for overall survival occurs at the date of last contact with the subject 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 on the mITT Population in Figures 14.2.3 and 14.2.4, respectively. Each figure will plot a two-sided 90% confidence band on the survival function, the median estimate for survival time, and a two-sided 90% confidence interval of the estimate of median survival time. The 90% confidence band on the survival function will use Greenwood's formula[2] to estimate the variance of the survival function. The 90% confidence interval of the median survival time will be computed using Brookmeyer and Crowley's method[1]. Each figure also will include the number of subjects in the risk set and the number of censored subjects computed at 3-month intervals.

8. SUMMARY OF CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

There are no changes to the planned analyses described in version 2.0 of the clinical trial protocol dated August 30, 2019.

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 groups. 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) columns will be continued on the following pages.

- "N" will represent the entire treatment group for the population 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 site, subject number, visit, and date/time (as applicable).

- All tables will be summarized for all subjects in aggregate and by phase and cycle where relevant.

- 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. Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics 1982;38:29-41.

2. Greenwood M. The natural duration of cancer. Reports on Public Health and Medical Subjects. London: Her Majesty's Stationery Office 1926;33:1-26.

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

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

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

APPENDIX 1. STUDY PROCEDURES AND ASSESSMENTS

1. All pre-study scans and biopsies should be done ≤ 6 weeks prior to registration.
2. All other pre-study assessments should be done ≤ 2 weeks prior to registration, unless otherwise noted.

Procedures	Screening	Cycle 1* (1 cycle=28 Days)					Cycle 2 and Subsequent Cycles*				Prior to Cycle 3 or 4	End of Treatment Visit[23]	Follow-Up[25]
		Day 1	Day 2	Day 8	Day 15	Day 22	Day 1	Day 2	Day 10	Day 11-28			
Windows (+/- days):	-28 to -1		1	1	1	1	3	1			7	14	
Administrative Procedures													
Written Informed Consent	X												
Disease Characteristics[1]	X												
Medical/Surgical History	X												
Assessment of Baseline Signs & Symptoms	X												
Prior and Concomitant Medication Review	X	X					X					X	
Clinical Procedures/Assessments													
Height	X												
Physical Exam including Weight	X	X					X					X	
Vital Signs (Temperature, Pulse, Blood Pressure)	X	X	X	X	X	X	X					X	
Body Surface Area (BSA)	X	X					X						
ECOG Performance Status	X	X					X					X	
Review Adverse Events		X		X	X	X	X					X[24]	
Laboratory Assessments													
CBC/Differential/Platelets[2]	X	X		X	X	X	X					X	
Chemistry[3]	X	X	X	X	X	X	X	X[4]				X	
Liver Function[5]	X	X					X					X	
LDH	X											X	

Procedures	Screening	Cycle 1* (1 cycle=28 Days)					Cycle 2 and Subsequent Cycles*				Prior to Cycle 3 or 4	End of Treatment Visit[23]	Follow-Up[25]
		Day 1	Day 2	Day 8	Day 15	Day 22	Day 1	Day 2	Day 10	Day 11-28			
Windows (+/- days):	-28 to -1		1	1	1	1	3	1			7	14	
Tumor Lysis Labs[6]		X	X	X	X	X	X	X[4]					
Beta-2 Microglobulin	X											X	
Hepatitis B and C Testing[7]	X												
Serum Pregnancy Test[8]	X												
Treatments[9]													
Oral Hydration[10]		X	X	X	X	X	X[10]						
Intravenous Hydration[11]		X					X[11]						
Venetoclax (dose in mg)[12]		20	20	50	100	200	400	400	400	0			
Bendamustine[13]		X	X				X	X					
Rituximab[14]		X					X						
Growth Factor Support[15]			X					X					
Subject Calendars													
Venetoclax Medication Diary		X	X	X	X	X	X	X	X				
Disease Assessments/Measurements													
PET/CT	X											X[16]	
Bone Marrow Biopsy & Aspirate	X											X[17]	
CT Chest/Abdomen/Pelvis											X[18]		
Disease and Survival Status											X	X	X
Correlative Study Samples													
Archived Tissue Procurement (Mandatory)[19]	X											X[20]	X[20]
Research Blood Specimens (Optional)[21]		X					X[21]					X	
MRD testing[22] (Mandatory)	X						X[22]					X	X

* **Scheduled Visits:** In general +/- 3 day window for therapy/tests/visits during therapy except as noted for TLS monitoring. Delay due to holidays, weekends, bad weather or other unforeseen circumstances will be permitted.

1. Record date of diagnosis, primary tumor type, histology, stage, and MCL international prognostic index (MIPI). MIPI calculator can be accessed using the European MCL Network website at http://www.european-mcl.net/en/clinical_mipi.php.
2. CBC with differential and platelet count which includes WBC, ANC, Platelets, Hgb, and Hct. Required prior to each dose of treatment, and results known prior to treatment administration.
3. BUN/creatinine, sodium, potassium, chloride, bicarbonate (HCO_3), glucose, and calcium. Refer to Section 5.4, Table 5-3 "Tumor Lysis Monitoring" in the clinical study protocol for additional time points and days not captured on Study Calendar.
4. Cycle 2, Day 2 only.
5. Albumin, total protein, alkaline phosphatase, AST, ALT, and total bilirubin.
6. Basic Metabolic Panel (Sodium, Potassium, Chloride, Bicarbonate (HCO_3), BUN, Creatinine, Calcium), Albumin, Uric Acid, and Phosphorus. Refer to Section 5.4, Table 5-3 "Tumor Lysis Monitoring" in the clinical study protocol for additional time points and days not captured on Study Calendar. See Appendix IV in the clinical study protocol for "Definitions of Tumor Lysis Syndrome".
7. Hepatitis B (HBV), Hepatitis B surface antigen (HBsAg), and Hepatitis C (HCV) testing within 6 weeks of registration. Patients who are chronic carriers of HBV with positive HBsAg+ and positive HCV serology are excluded. Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are allowed with protective hepatitis B surface antibody AND a negative hepatitis B viral load by PCR. If enrolled, patients must be willing to undergo monthly HBV DNA testing.

   Patients with positive HCV antibody must be negative for HCV by PCR to be eligible for study participation. Prior treatment for an active hepatitis C infection will be allowed so long as the hepatitis C viral load by PCR is negative.
8. Required for females of child-bearing potential.
9. Standard pre-medications and antiemetic therapy per institutional guidelines are allowed per Section 5.1 of the clinical study protocol. Also, refer to Section 5.3 in the clinical study protocol for details on prophylaxis for TLS.
10. Encourage at least 2 liters of oral fluids per day starting 24 hours prior to Cycle 1, Day 1 and continuing until Cycle 2, Day 10. Refer to Section 5.3 in the clinical study protocol for details.
11. At least 1 liter of IV hydration should be given on Day 1 of Cycle 1 and Cycle 2. Additional IV fluids and monitoring for TLS is allowed per treating physician discretion. Refer to Section 5.3 in the clinical study protocol for details.
12. Venetoclax will be administered orally. **Cycle 1:** 20 mg on Day 1-7; 50 mg on Day 8-14; 100 mg on Day 15-21; and 200 mg on Day 22-28. **Cycle 2-6:** 400 mg on Day 1-10. One cycle = 28 days. On days when venetoclax is given with additional anti-lymphoma agents, venetoclax should be given first. See Section 5 of the clinical study protocol for dosing instructions and tumor lysis prophylaxis/monitoring and Section 6 of the clinical study protocol for dose delays/modifications.
13. Bendamustine is given as 90 mg/m_2 IV day 1 and 2 before or after rituximab. See Section 5 of the clinical study protocol for dosing instructions and Section 6 of the clinical study protocol for dose delays/modifications.
14. Rituximab 375 mg/m^2 is given on Day 1 of each cycle before or after bendamustine. If the first two cycles of rituximab are well tolerated, IV rituximab may be replaced with 1400 mg/23,400 units SQ rituximab/hyaluronic acid on Day 1 of Cycles 3-6, per investigator and patient preference. See Section 5 of the clinical study protocol for dosing instructions and Section 6 of the clinical study protocol for dose delays/modifications.

NOTE: After 6 cycles of venetoclax, bendamustine and rituximab, subjects responding to therapy may receive maintenance rituximab (one dose every 8 ± 2 weeks for 12 doses or 24 months whichever comes first) per physician and patient preference.

15. Growth factor support should be given 24-72 hours after the last dose of bendamustine for each cycle per Section 5.5 of the clinical study protocol.
16. PET/CT 6-8 weeks after Day 1 of last completed cycle. Each target lesion should have Deauville score at end of treatment. Refer to Section 9.2, Table 9-1 and Appendix V in the clinical study protocol for details.
17. Bone marrow biopsy and aspirate per standard of care. Mandatory sample submission for research when collected per standard of care.
18. Repeat imaging before Cycle 3 or 4 per institutional guidelines. CT scans or PET/CT scans may be used at this time point per institution standards. Any progression should be confirmed by PET/CT.
19. Pre-treatment, diagnostic pathology specimens (organ or lymph node biopsy or excision) obtained in the course of standard biopsy or surgery (if sufficient tissue is available, submission is mandatory). Formalin-Fixed Paraffin-Embedded (FFPE) blocks and 5 FFPE slides or up to 15 FFPE slides plus H&E slide (if tissue is limited, then minimum of 10 slides) will be required. Procurement of tissue will be mandatory for enrollment, but if additional tissue from initial biopsy is not available, repeat biopsy will not be required. **Optional:** Any leftover tissue banked for future research. See Section 13.1 of the clinical study protocol and the PrE0405 Lab Manual for details.

    NOTE: If blocks and/or slides are unavailable and bone marrow is involved with mantle cell lymphoma, obtain two 2 mL EDTA tubes of bone marrow aspirate (one for baseline MRD analysis and one for future research). If blocks/slides and bone marrow are unavailable and peripheral blood is involved with mantle cell lymphoma obtain one 4 mL and one 6 mL EDTA tubes of peripheral blood (one for baseline MRD analysis and one for future research). If baseline samples (blocks/slides, bone marrow, and/or peripheral blood) are not submitted at baseline for MRD (i.e., not involved with mantle cell lymphoma), then patients will be allowed to remain on study but MRD samples will not be collected during the study.

20. **Optional:** At time of progression, biopsy and peripheral blood samples are requested to be sent for correlative studies and banked for future research. See Section 13.1 of the clinical study protocol and the PrE0405 Lab Manual for details.
21. **Optional Research Bloods:** See Section 13.3 in the clinical study protocol and the PrE0405 Lab Manual for details.

    Cycle 1, Day 1 (prior to treatment)
    Peripheral Blood: One 10 mL red top tube and one 6 mL in EDTA tube

    Cycle 2, Day 1 (prior to treatment)
    Peripheral Blood: One 10 mL red top tube and one 6 mL in EDTA tube

    Cycle 4, Day 1 (prior to treatment)
    Peripheral Blood: One 10 mL red top tube and one 6 mL in EDTA tube

    End of Treatment Visit
    Peripheral Blood: One 10 mL red top tube and one 6 mL in EDTA tube

    At Time of Progression
    Peripheral Blood: One 10 mL red top tube, one 4 mL and one 6 mL in EDTA tube

22. **Mandatory MRD Samples:** See Sections 13.1, 13.2, and 13.3 of the clinical study protocol and the PrE0405 Lab Manual for details.

    Screening/Study Entry
    FFPE: 3-5 FFPE slides from lymph node (preferred)

    NOTE: If FFPE unavailable, either bone marrow aspirate (2 mL EDTA tube) or peripheral blood (4 mL EDTA tube) are acceptable as long as they are involved with mantle cell lymphoma. If baseline samples (blocks/slides, bone marrow, and/or peripheral blood) are not submitted at baseline for MRD (i.e., not involved with mantle cell lymphoma), then patients will be allowed to remain on study but MRD samples will not be collected during the study.

End of Treatment Visit
Peripheral Blood: One 4 mL in EDTA tube
Bone Marrow Aspirate (per standard of care)*: One 2 mL in EDTA tube

*Bone Marrow Aspirate: Submission is mandatory when collected per standard of care.

23. 6-8 weeks after Day 1 of last completed cycle.
24. Patients will be followed for adverse events for 30 days after their last dose of study medication.
25. Every 3-6 months or per institutional guidelines for up to 5 years from treatment discontinuation for progression and survival. Imaging to be done per institution standards and/or physician discretion. Maintenance rituximab is allowed and will be documented but will not constitute additional therapy. Initiation of first anti-cancer therapy will also be documented.

NOTE: 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 with the exception of allowed maintenance rituximab for up to 5 years or study closure.

DOCUMENT HISTORY

Version Date	Modified By	Summary of Changes