Statistical Analysis Plan

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Phase II Study of Venetoclax (ABT-199/GDC-0199) in Combination with Obinutuzumab and Bendamustine in Patients with High Tumor Burden Follicular Lymphoma as Front Line Therapy

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LIST OF ABBREVIATIONS

Abbreviation/Acronym	Definition
AE	Adverse event
ALC	Absolute Lymphocyte Count
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
Bcl-2	B-cell lymphoma 2
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
ECOG	Eastern Cooperative Oncology Group
FFPE	Formalin-Fixed Paraffin-Embedded
FISH	Fluorescence in Situ Hybridization
FLIPI	Follicular Lymphoma International Prognostic Index
GELF	Groupe D'Etude des Lymphomes Follicularies
H&E	Hematoxylin & Eosin
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
Hct	Hematocrit
HCV	Hepatitis C virus
Hgb	Hemoglobin
IgG	Immunoglobulin G
IHC	Immunohistochemistry
ITT	Intent-to-Treat Population
IV	Intravenous
kg	kilograms
LDH	Lactate Dehydrogenase
Mcl-1	Myeloid cell lymphoma-1

MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
mg/m^2	Milligrams per square meter of body surface area
mITT	Modified Intent-to-Treat Population
mRNA	Messenger ribonucleic acid
msec	Milliseconds
ORR	Objective 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
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
TLS	Tumor lysis syndrome
Un	Unevaluable
WBC	White Blood Cells
WHO	World Health Organization

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 Objective

- To estimate the proportion of patients achieving a complete remission (CR) at the end of induction with the combination of venetoclax, obinutuzumab, and bendamustine

2.2. Secondary Objectives

- To determine the ORR of patients treated
- To determine the proportion of patients who achieve a PR with induction therapy and later convert to CR with maintenance therapy
- To evaluate PFS and OS in the intent to treat (ITT) population
- To evaluate the compliance and toxicities of patients receiving induction and maintenance therapy

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

- To compare Bcl-2 protein expression by immunohistochemistry (IHC) in pre-treatment biopsies with response, PFS, and OS
- To assess Bcl-2 family expression by mRNA expression including ratios of Bcl-2/BIM, Bcl-2/Mcl-1 and others with response, PFS, and OS

- To compare BCL2 rearrangement status by fluorescence in situ hybridization (FISH) in pretreatment biopsies and correlate with response, PFS, and OS
- To compare Mcl-1 and Bcl-XL protein expression by IHC in pretreatment biopsies with response, PFS, and OS
- To compare histologic features of pretreatment biopsies with response, PFS, and OS

2.4. Study Endpoints

2.4.1. Efficacy Endpoints

- Incidence of Complete Response (CR) during the induction phase
- Objective Response Rate, over both induction and maintenance phases
- Overall Survival (OS)
- Progression-Free Survival (PFS)

2.4.2. Safety Endpoints

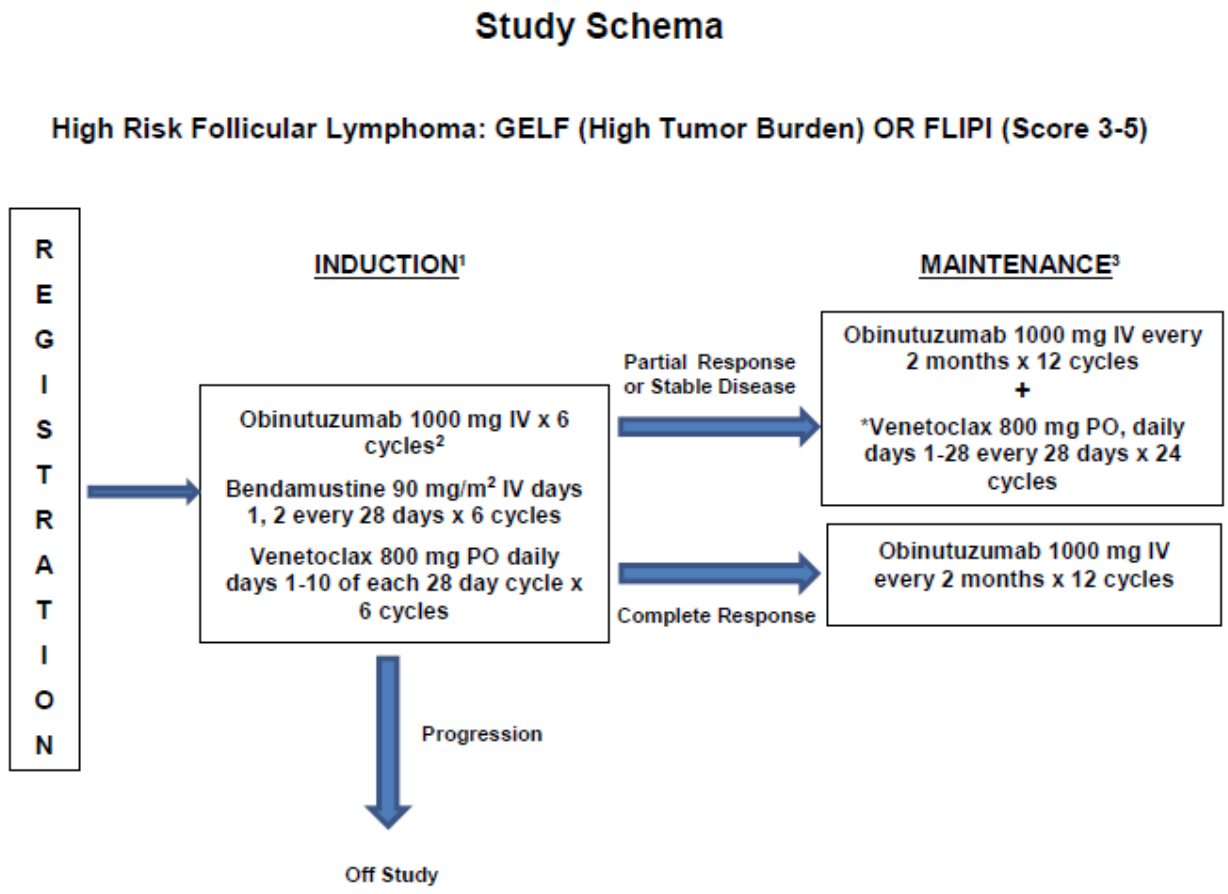
- Adverse events, including
    - Percentage of subjects with treatment-related events of CTCAE grade 3 or higher
    - Percentage of subjects with events of special interest
    - Percentage of subjects withdrawn due to AEs
- Dose compliance
- Hematology and Chemistry Laboratory Assessments

3. STUDY DESIGN

3.1. Study Design

This is a single-arm phase II clinical trial in adult male and female subjects with a histologically confirmed (biopsy-proven) diagnosis of follicular B-cell non-Hodgkin lymphoma and a high tumor burden (higher risk) as defined by either the GELF (Groupe D'Etude des Lymphomes Follicularies) or FLIPI (follicular lymphoma international prognostic index) criteria. Eligible patients will receive induction therapy with venetoclax, obinutuzumab, and bendamustine for six cycles. For patients without progressive disease, the induction phase will be followed by a maintenance phase in which patients who achieve a complete response (CR) will receive obinutuzumab every 2 months for a total of 12 cycles and patients who achieve partial response (PR) or stable disease (SD) will likewise receive obinutuzumab every 2 months for a total of 12 cycles, but accompanied by venetoclax therapy for the 12 cycles. More details on the treatment schedule can be found in the schema below:

Figure 1 Study Schema



Accrual goal: 56 patients

Cycle length: 28 days (4 weeks)

[1] There will be a formal, detailed toxicity evaluation after 28 patients complete 3 cycles of treatment (including patients that come off treatment for any reason). Section 12.1 for details.

[2] Cycle 1 only obinutuzumab: 100 mg IV will be given on day 1 and 900 mg will be given on day 2. Cycle 1, day 8 and day 15, 1000 mg IV will be given. Starting with cycle 2 obinutuzumab 1000 mg will be given on Day 1 only.

[3] Patients will move on to the maintenance phase no earlier than 8 weeks and no later than 12 weeks post completion of cycle #6, day 28 of induction therapy.

* Patients subjected to venetoclax dose reductions during induction phase, will continue with the same dosing during maintenance therapy.

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 every 3 cycles (12 weeks) during the induction phase and every 6 months during the maintenance phase. Tumor response will be assessed by the investigator in accordance with Cheson criteria. Subjects who discontinue treatment in the absence of progression will continue to have tumor assessments until documented progression or initiation of alternate anti-cancer therapies.

3.2. Study Duration

The study will consist of 3 periods: an Induction Treatment Period (6 cycles of 28 days each), followed by a Maintenance Treatment Period (Patients with CR = every 2 months for 12 cycles; patients with SD or PR = every 28 days for 24 cycles), and a Follow-up Period (2 years from date of last study treatment or study closure) to monitor survival status, disease progression, and initiation of new cancer therapies. Maintenance therapy will start between 8 and 12 weeks following the end of the last induction therapy cycle. Therefore, the total duration of the study for each subject will be a maximum of 4.75 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, or investigator determination that protocol requirements are detrimental to subject health.

3.3. Study Population

A total of 56 patients will be enrolled into the study, 51 of which are expected to be eligible and treated. Patients will be recruited from multiple US clinical sites. Patients who discontinue from the study will not be replaced.

The study population will consist of adult males and females with a histologically confirmed (biopsy-proven) diagnosis of follicular B-cell non-Hodgkin lymphoma. The stage of the disease at Screening must be II, III, or IV according to Modified Ann Arbor staging. Patients must meet criteria for High Tumor Burden (higher risk) as defined by either the GELF or FLIPI criteria, have adequate organ function, and no prior chemotherapy, radiology, or immunotherapy for lymphoma.

3.4. Randomization and Blinding

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

3.5. Treatment Administration

Eligible patients will receive induction therapy with venetoclax, obinutuzumab, and bendamustine for six cycles of twenty-eight days each. An 800 mg oral dose of venetoclax will be dispensed on Days 1-10 of each 28 day induction cycle. In the first induction cycle, patients at high risk of tumor lysis syndrome (TLS) venetoclax will be administered on Days 8-14 instead. Dose compliance will be monitored via a pill diary. In the first induction cycle, obinutuzumab will be administered as 100 mg on day 1, 900 mg on day 2, and 1000 mg on each of days 8 and 15. In all subsequent induction cycles, obinutuzumab dosing will consist of a single 1000 mg IV administration on day 1 only. Bendamustine will be administered to patients as a 90 mg/m^2 IV infusion on days 1 and 2 of each 28-day induction cycle.

Maintenance treatment will begin 8-12 weeks after the end of the last induction cycle. Patients with progressive disease will not continue on the maintenance arm. Patients who achieve a complete response (CR) at the end of the induction phase will receive a 1000 mg IV of obinutuzumab every 2 months for a total of 12 cycles. Patients who achieve partial response (PR) or stable disease (SD) at the end of the induction phase will receive a 1000 mg IV of obinutuzumab every 2 months for a total of 12 cycles and will take a daily 800 mg oral tablet of venetoclax for 24 cycles of 28 days each. If the dose of venetoclax as reduced during the induction phase, the same reduced dose will continue to be taken during the maintenance phase.

In the event that venetoclax is not well-tolerated in the induction phase, the dose will be reduced from 800 mg on days 1-10 to 800 mg on days 1-5 (Dose Level -1). If dose level -1 is not well-tolerated either, the dose will be reduced to 400 mg on days 1-5 (Dose Level -2). Patients who do not tolerate dose level -2 will be discontinued from all study treatment. In the event that bendamustine is not well-tolerated in the induction phase, the dose will be reduced to 70 mg/m^2. Patients will be removed from all study treatment if they require a dose reduction of bendamustine below 70 mg/m^2.

Acetaminophen (650 or 1000 mg orally) and diphenhydramine (25 or 50 mg oral or intravenous) will be administered 30 to 60 minutes prior to starting each infusion of obinutuzumab or per institutional guidelines. Since transient hypotension may occur during obinutuzumab infusion, consideration is to be given to withholding anti-hypertensive medications 12 hours prior to obinutuzumab infusion.

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 objective of this study is complete response (CR) after induction. We anticipate a 50% CR rate after induction treatment with obinutuzumab and bendamustine. With the addition of venetoclax (given concurrently), a CR rate of 65% (15% improvement from 50%) would be considered promising for the addition of venetoclax to the induction regimen. A total of 56 patients will be enrolled into the study, 51 of which are expected to be eligible and treated. Among 51 eligible, treated patients, this study will have the desired 85% power to detect a 15% improvement in CR using a one-sided exact binomial test.

4.2. Methodology

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

Post-dose safety parameters will be summarized in aggregate for all subjects. Induction phase data will not be presented in separate tables from maintenance phase data. For tables summarizing change from baseline for laboratory data, baseline will be defined as the last non-missing result prior to the subject's first study dosing of venetoclax, bendamustine, or obinutuzumab. 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. Percentages will be computed using the number of subjects in the relevant analysis population as the denominator unless stated otherwise.

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

There will be a formal, detailed, toxicity evaluation after 28 patients (50% of accrual target), including patients who terminate treatment for any reason, have been enrolled and have been on the study for the period of 3 cycles. For all treatment-related Grade 3 or higher AEs, the formal evaluation will be done within each AE category and also for the overall AE rate.

It is expected that the proportion of any CTCAE v5.0 toxicity grade 3 or higher, treatment-related adverse event will be no greater than 35% for each MedDRA system organ class or preferred term. If the proportion of patients who experienced a Grade 3 or higher, treatment-related, adverse event for a given preferred term or system organ class is greater than 45% (~13 or more of 28 patients), a detailed review of all treatment-related adverse events will be conducted, and the study review team may decide if treatment modification is necessary. If the true proportion of patients with an adverse event within a given system organ class or preferred term is 55% or greater, then there is at least 93% probability of exceeding the observed adverse event boundary at interim. Conversely, if the true proportion of patients with an adverse event within a given system organ class or preferred term is 35% or less, then there is only 25% probability of crossing the toxicity boundary at interim. The above decision boundary (45% or more observed events) will be followed for all Grade 3 or higher, treatment-related events within each system organ class and preferred term.

The expected overall toxicity rate, considering all Grade 3 or higher, treatment-related adverse events across all MedDRA system organ classes and preferred terms, is approximately 40%. If proportion of patients who experienced any Grade 3 or higher, treatment-related adverse event is higher than 50% (14 or more out of 28 patients), a detailed review of all treatment-related adverse events will be conducted, and the study review team may decide if treatment modification is necessary. If the true proportion of patients with any such event is 60% or higher, then there is at least 90% probability of exceeding the observed boundary at interim. Conversely, if the true proportion is 40%, then there is only a 19% chance of crossing the toxicity boundary at interim. This decision boundary will be followed for the overall incidence of any Grade 3 or higher, treatment-related adverse event.

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. This study has a single primary objective which is tested via a single hypothesis test. The formal, detailed toxicity evaluation at interim will consist of applying decision rules to three categories of adverse events. No adjustment for

multiplicity will be made; the evaluation is intentionally conservative. The three categories of adverse events being evaluated are subsets of one another, which reduces the need for multiplicity adjustments.

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 the Intent-to-Treat Population, Safety Population, or Modified Intent-to-Treat (mITT) Population.

4.7.1. Intent-to-Treat Population

The ITT Population will consist of all enrolled subjects. Kaplan-Meier curves for the secondary enpoints of progression-free survival and overall survival will be created on the ITT population.

4.7.2. Safety Population

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

4.7.3. 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, completing the study, and discontinuing treatment will be tabulated (Table 14.1.1). Subjects discontinuing treatment will be categorized by reason for discontinuation.

5.2. Demographics and Baseline Characteristics

Demographic data (age, sex, and race) and screening characteristics (WHO tumor grade, FLIPI-1 and FLIPI-2 scores, number of GELF criteria met, ECOG performance status, presence/absence of bone marrow involvement, lymph node and metastasis staging, and Ann Arbor staging – including presence/absence of B symptoms) for all subjects will be listed (Listing 16.2.4). These data, in addition to ethnicity, height, weight, body surface area, and the proportion of subjects meeting each individual FLIPI-1, FLIPI-2 and GELF criterion at screening, will be summarized for the ITT Population, Safety Population, and mITT Population (Table 14.1.2). Descriptive statistics (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, dose compliance, and hematology and chemistry laboratory testing. 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. If any pre-baseline safety data are repeated for a given visit time point, the measurement taken closest to the first study treatment dosing will be used in the analysis. Baseline will be defined as the last non-missing result, including results from repeated measurements, before the first study dosing. If there are repeated measurements at a time point after the first study treatment dosing, the earliest assessment at that time point will be used in the summary tables.

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, the event 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 subjects who experience TEAEs will be summarized. This summary will also be subdivided in the same table by seriousness, CTCAE v5.0 toxicity grade, outcome, relation to each of the three study medications, and whether or not 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), study discontinuation, or fits the "special interest" category defined in the study protocol (Table 14.3.1.1).

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 20.1 (Table 14.3.1.2). An event will be considered to be treatment-related if it is assessed by the investigator as related, probably related, or possibly related to any of the three study treatments. 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. The set of all treatment-related AEs with toxicity grade of three or greater also will be listed by subject (Listing 16.2.7). The listing will all include MedDRA (version 20.1) system organ class and preferred term, the date and time 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, toxicity grade, any criteria met for classification as a serious adverse event, and whether or not the event meets the "special interest" criteria defined in the protocol. This table and listing are designed to be used at the interim toxicity evaluation after 28 subjects have been enrolled and each either have completed three cycles of induction therapy or discontinued study treatment.

Separate tables will be used to count by system organ class and preferred term subjects who experience treatment-emergent AEs with toxicity grade of three or greater, regardless of relationship to the study

treatments (Table 14.3.1.3), and treatment-emergent adverse events of special interest (Table 14.3.1.4). These tables, too, 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.

6.2. Study Drug Administration and Dose Compliance

The number of induction cycles in which any of the three study treatments were administered will be tabulated 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 and phase (induction vs. maintenance) with counts and percentages based on the number of subjects who received at least one dose of the given treatment during the given phase. The number of scheduled venetoclax dosings missed per cycle will be summarized with descriptive statistics (n, mean, standard deviation, median, minimum, maximum) by study phase. Also to be summarized with descriptive statistics is the cumulative dose of obinutuzumab and bendamustine by study phase and the duration of all-treatment exposure in the maintenance phase.

6.3. Clinical Laboratory Data

Shift tables presenting toxicity grade changes from baseline for hematology (Table 14.3.6.1) and chemistry (Table 14.3.6.2) laboratory results will be created. For each laboratory test, the shift tables will tabulate subjects by their toxicity grade, or lack thereof, at baseline, and their worst toxicity grade observed at any post-baseline assessment during either treatment phase. Baseline is defined as the latest non-missing result prior to the first study dosing with venetoclax, obinutuzumab, or bendamustine.

7. EFFICACY ANALYSIS

The efficacy analyses are designed to evaluate CR rates according to the Cheson criteria during both treatment phases of this study and to evaluate survival and progression of disease during both this study and the subsequent two-year follow-up period. All efficacy endpoints are evaluated for either the Intent-to-Treat (ITT) or Modified Intent-to-Treat (mITT) Population.

7.1. Primary and Secondary Efficacy Endpoint Analyses

The **primary endpoint** in this study is the proportion of treated subjects who achieve a complete response (CR) at any disease response assessment during the induction phase. This proportion will be computed for the mITT Population and presented along with the Clopper-Pearson exact 90% confidence interval of the proportion, expressed as a percent (Table 14.2.1). The same table will show the proportion of subjects in the mITT Population whose best overall disease response during induction treatment phase is a partial response (PR), stable disease (SD), and 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 subjects who do not have a valid disease response assessment during the induction phase for any reason, including termination of study treatment prior to a subject's first on-treatment disease response assessment during the induction phase. One of the **secondary endpoints** of the study is the proportion of treated subjects whose best overall response during induction phase was a partial response and who then later achieved a complete response at any re-staging assessment after the start of the maintenance phase. This proportion will be computed for the mITT Population along with the 90% Clopper-Pearson exact confidence interval for the proportion, expressed as a percent, and will be included in Table 14.2.1. A listing of the best overall response during induction and the best overall response during maintenance by subject also will be generated for the mITT Population to support evaluation of this secondary endpoint (Table 14.2.2).

Another **secondary endpoint** of the study is the Objective Response Rate across both induction and maintenance treatment phases. Objective Response Rate is defined as the proportion of treated subjects who achieved a partial response (PR) or complete response (CR) at any disease response assessment over the course of the study – both treatment phases considered together. The Objective Response Rate will be computed for the mITT Population and will be presented along with the 90% Clopper-Pearson exact confidence interval of the proportion expressed as a percent (Table 14.2.3). The table will also present the best overall disease response, i.e., CR, PR, SD, PD, or Un, across all induction and maintenance phase assessments and a summary of the duration of objective response in months among the subjects who attained a PR or CR in either treatment phase. The summary of objective response duration will use descriptive statistics (n, mean, standard deviation, median, minimum, and maximum).

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 number and percent of subjects who experience the corresponding events for PFS and OS and the number of subjects censored for each endpoint will be summarized along with the Kaplan-Meier median survival times and corresponding 90% confidence intervals (Table 14.2.4). The 90% confidence intervals will be computed using Greenwood's formula. The Kaplan-Meier survival curves for progression-free survival and overall survival will be presented on the mITT Population in Figures 14.2.7 and 14.2.9, respectively, and on the ITT Population in Figure 14.2.8 and Figure 14.2.10, respectively.

The assessment results for disease response (Listing 16.2.6.1) and target lesion size (Listing 16.2.6.2) will be listed by site, subject, 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 in Table 14.2.5 for each induction phase assessment along with the best target, non-target, and overall response observed during induction, maintenance, and induction and maintenance considered in aggregate. The best target lesion response is also shown graphically in Figure 14.2.6. The figure represents each subject'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 subject'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).

8. SUMMARY OF CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

There are no changes to the planned primary and secondary endpoint analyses described in version 4.0 of the clinical trial protocol dated January 23, 2018.

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. 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 ≤ 10 weeks prior to registration.
2. All other pre-study assessments should be done ≤ 4 weeks prior to registration, unless otherwise noted.

Procedures	Screening	Cycle 1* (1 cycle=28 Days)					Cycles 2-6*		Every 3 Cycles (every 12 weeks)	Maintenance[17]*	Follow-Up[18]
		Day 1	Day 2	Day 8	Day 15	Day 21 Break	Day 1	Day 2			
Written Informed Consent	X										
Documentation of GELF, FLIPI and FLIP2 criteria[1]	X										
Medical/Surgical History	X										
Assessment of Baseline Signs & Symptoms	X										
Height in cm	X										
Physical Exam	X	X		X	X		X			X	
Weight in kg	X	X					X			X	
Vital Signs (Temperature, Pulse, Blood Pressure)	X	X		X	X		X			X	
Body Surface Area (BSA)	X	X					X			X	
Performance Status	X	X					X			X	
CBC/Differential/Platelets[2]	X	X	X	X	X		X			X	
Chemistry[3]	X	X		X			X			X	
Hepatitis B & C Testing[4]	X										
Beta-2 Microglobulin	X										

Procedures	Screening	Cycle 1* (1 cycle=28 Days)					Cycles 2-6*		Every 3 Cycles (every 12 weeks)	Maintenance[17]*	Follow-Up[18]
		Day 1	Day 2	Day 8	Day 15	Day 21 Break	Day 1	Day 2			
Immunoglobulin (IgG)[5]	X								X[5]	X[5]	
Serum or Urine Pregnancy Test[6]	X										
Tumor Lysis Labs[7]		X	X								
PET CT[8]	X								X[9]	X[10]	
Chest, Abdomen, and Pelvic CT with Contrast[8]									X	X[10]	
Bone Marrow Biopsy	X								X[11]		
Archived Tissue Procurement (Mandatory)[12]	X						X[13]			X[13]	X[13]
Induction Treatment Administration[14]		X	X	X	X		X	X			
Maintenance Treatment Administration[15]										X	
Concomitant Medication Review	X	X	X	X	X		X	X		X	
Adverse Events Assessment		X	X	X	X		X	X		X[16]	
Survival Status											X

*** Scheduled Visits:** The cycle length may be altered to -2 days or to +3 days for holidays or other extenuating scheduling situations.

1. Record the GELF, FLIPI-1 (Appendix VII) and FLIPI-2 criteria (Appendix VIII).
2. CBC with differential and platelet count which includes WBC, ANC, Platelets, Hgb, and Hct. Required prior to each dose of chemotherapy (days 1, 2, 8 and 15 of cycle 1 and day 1 of cycle 2 and subsequent cycles), and results known prior to treatment administration.
3. Albumin, BUN/creatinine, uric acid, sodium, potassium, chloride, glucose, calcium, alkaline phosphatase, AST, ALT, total bilirubin, LDH and total protein.
4. 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) may be included if HBV DNA is undetectable. If enrolled, patients must be willing to undergo monthly HBV DNA testing. Patients with positive HCV antibody must be negative for HCV by polymerase chain reaction (PCR) to be eligible for study participation.
5. Obtain quantitative immunoglobulins at end of induction and every 6 months during maintenance therapy.
6. Required for females of childbearing potential within 2 weeks of registration.
7. Labs for tumor lysis: Cycle 1, day 1- add phosphorus to above chemistries. Cycle 1, day 2- BUN/creatinine, uric acid, sodium, potassium, chloride, glucose, calcium, phosphorus and LDH need to be obtained on all patients. Patients who are at high risk of tumor lysis (e.g., any lymph mass ≥ 10 cm on the screening CT scan, Absolute Lymphocyte Count (ALC) >25 x 10^9; Section 6.3.2 Prophylaxis and Guidelines for Hospitalization due to TLS Risk for additional details) or as determined by the treating physician may be admitted to the hospital to be monitored for tumor lysis. Patients at high-risk for TLS will start venetoclax on Cycle 1, day 8 (daily for 7 days total). Information on prophylaxis for TLS and/or if patients experiences tumor lysis refer to Section 6.3.2 and Appendix V.

   NOTE: On Cycle 1, Day 8 for high risk TLS patients, vital signs will be measured and serum chemistry and hematology samples will be drawn before venetoclax dosing, and at 8, 12 and 24 hours post dose (8, 12 and 24 hour blood samples are mandated only if patient is hospitalized). These samples are to be sent immediately to the laboratory and the investigator or designee must review the results promptly. Laboratory values obtained before the dose of venetoclax are to be used to determine whether a patient developed a change related to TLS. Laboratory results of the 24-hour post dose must be reviewed before receiving the dose of venetoclax for that day
8. PET/CTs are the preferred imaging modality. Notably however, once a patient enters complete remission, then only CT's (chest/abdomen/pelvis) should be obtained (not both PET/CT and dedicated CTs) except as noted in footnote #9 below. MRI exams of the chest/abdomen/pelvis may be performed, if CTs of the chest/abdomen/pelvis cannot be obtained.
9. PET/CT to be obtained after cycle 6 (not required after cycle 3). CT of the chest/abdomen/pelvis will suffice at interim restaging i.e., after cycle 3.
10. Performed every 6 months or as per standard of care.
11. Performed after cycle 6. Bone marrow biopsy at the end of induction treatment needs to be obtained only if it was positive prior to initiation of therapy.
12. Pre-treatment, diagnostic pathology specimens obtained in the course of standard biopsy or surgery (if sufficient tissue is available, submission is mandatory): Formalin-Fixed Paraffin-Embedded (FFPE) blocks and 7-10 FFPE slides or if blocks are not available, up to 25 FFPE slides plus H&E slide (if tissue is limited, then minimum of 13 slides) will be required. Procurement of tissue will be mandatory for enrollment (submission of tissue is not required prior to registration), but if additional tissue from initial biopsy is not available, repeat biopsy will not be required (no biopsy should be performed solely for the purposes of obtaining research samples).
13. **Optional**: Any tumor biopsy samples obtained during treatment or post-treatment (Formalin-Fixed Paraffin-Embedded (FFPE) blocks or up to 15 FFPE slides plus H&E slide) will be requested for research and any leftover tissue (pre-treatment, during treatment or post-treatment) will be banked for future research. See Section 13.1 for details.

14. Venetoclax will be administered orally as continuous dosing days 1-10 of each 28 day cycle (except for patients with high risk of developing TLS, will start venetoclax on day 8 of cycle 1 of therapy for a total of 7 days). On days when venetoclax is given with additional anti-lymphoma agents, venetoclax should be given first. Patients will receive obinutuzumab by IV infusion on Cycle 1, days 1, 2, 8, and 15 of 28 day cycle and Cycles 2-6 on day 1 of each 28 day cycle (1 cycle=28 days). Bendamustine will be administered on days 1, 2 of each cycle. See Section 5 for dosing instructions and Section 6 for dose delays/modifications.
15. The maintenance phase will start no earlier than 8 weeks and no later than 12 weeks following completion of cycle 6, day 28 of induction therapy (patients who do not start maintenance therapy by week 12 will be removed from study). During the maintenance phase, patients who are in a complete remission will receive obinutuzumab every 2 months for a total of 12 cycles. Patients who are in a PR or stable disease will receive venetoclax and obinutuzumab for a total of 24 cycles and 12 cycles, respectively. Patients who receive venetoclax (orally as continuous dosing days 1-28) and obinutuzumab (obinutuzumab will be given every 8 weeks) will be seen every month (to dispense venetoclax). On days when venetoclax is given with additional anti-lymphoma agents, venetoclax should be given first. (Patients on both venetoclax and obinutuzumab who convert to CR, will remain on both venetoclax and obinutuzumab for a total of 24 cycles and 12 cycles respectively.)

    NOTE: If venetoclax was dose reduced during the induction phase, the same dose reduction will continue during the maintenance phase.
16. Adverse events will be captured for 30 days after their last dose of study medication.
17. Patients who receive obinutuzumab only will be seen every 2 months with indicated exams/testing performed. Patients who receive obinutuzumab and venetoclax will be seen every month with indicated exams/testing performed.
18. Every 6 months for up to 2 years from treatment discontinuation or until study closure. 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.

DOCUMENT HISTORY

Version Date	Modified By	Summary of Changes