BeiGene

STATISTICAL ANALYSIS PLAN

Study Protocol Number:	BGB-3111-213
Study Protocol Title:	A Phase 2 Study to Assess the Safety, Tolerability, and Activity of BGB-3111 in Combination with Rituximab in Chinese Patients with Relapsed/Refractory Diffuse Large B-Cell Lymphoma (non-GCB Subtype) and Relapsed/Refractory Indolent Lymphoma (Follicular Lymphoma and Marginal Zone Lymphoma)
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AEs	adverse events
AESI	adverse event of special interest
BOR	best overall response
CMR	complete metabolic response
CR	complete response
CT	computed tomography
DLBCL	diffuse large B-cell lymphoma
FL	follicular lymphoma
GCB	germinal center B-cell-like
MedDRA	medical dictionary for regulatory activities
MZL	marginal zone lymphoma
NCI CTCAE	national cancer institute common terminology criteria for adverse events
ORR	overall response rate
PD	progressive disease
PFS	progression-free survival
PK	Pharmacokinetics
PT	preferred term
R/R	relapsed/refractory
SMC	safety monitoring committee
SOC	system organ class
TEAE	treatment emergent adverse event

1 INTRODUCTION

The purpose of this statistical analysis plan is to describe the detailed plan for data analysis in evaluation of safety and efficacy of zanubrutinib (BGB-3111) in combination with rituximab for BGB-3111-213. The focus of this statistical analysis plan is for the planned final analysis specified in the study protocol. This document is based on the protocol version 2.0 dated 28-MAR-2019.

Any changes made to the planned analyses that are in the protocol prior to database lock will be identified and documented in statistical analysis plan and clinical study report. The changes made to the planned analyses after database lock will be only documented in the clinical study report.

2 STUDY OVERVIEW

This is a multicenter open-label study evaluating the safety and efficacy of zanubrutinib 160 mg twice daily in combination with rituximab in the following patients:

- Cohort 1 (planned: n=20): relapsed/refractory (R/R) non-germinal center B-cell-like (GCB) diffuse large B-cell lymphoma (DLBCL)
- Cohort 2 (planned: n=20): R/R follicular lymphoma (FL) or R/R marginal zone lymphoma (MZL)

Rituximab will be administered at 375 mg/m^2 intravenously on Cycle 1 Days 1, 8, 15, 22, and on Day 1 of Cycles 4, 6, 8, 10.

Zanubrutinib will be administered continuously at 160 mg orally twice daily since Day 1 of Cycle 1. Zanubrutinib will be administered at least 30 minutes prior to the initiation of the rituximab infusion. One cycle will be 28 days.

Treatment with zanubrutinib may be continued for up to 2 years total treatment, until disease progression or an unacceptable toxicity occurs. Rituximab is continued for a total of 8 doses or until disease progression or an unacceptable toxicity. Patients may withdraw from study treatment due to an adverse event, disease progression, or withdrawal of consent. For patients still on study drug at the time of study closure and continuing to benefit from study drug, the sponsor will make zanubrutinib monotherapy available for continued treatment in a long-term extension study.

The continuous safety evaluation of this study will be performed by a Safety Monitoring Committee (SMC) as outlined in the SMC charter.

Pharmacokinetics blood sampling for zanubrutinib will be performed at: (1) pre-dose on Cycle 1 Day 1; (2) 2 hours (± 30 minutes) after zanubrutinib dosing on Cycle 1 Day 1; (3) pre-dose on Cycle 4 Day 1; and (4) 2 hours (± 30 minutes) after zanubrutinib dosing on Cycle 4 Day 1. Pharmacokinetics blood sampling for rituximab will be performed at (1) pre-dose on Cycle 1 Day 1; (2) within 30 minutes after end of infusion on Cycle 1 Day 1; (3) pre-dose on Cycle 4 Day 1; (4) within 30 minutes after end of infusion on Cycle 4 Day 1.

3 STUDY OBJECTIVES

All primary and secondary objectives will evaluate zanubrutinib plus rituximab in patients with R/R non-GCB DLBCL, R/R FL, and R/R MZL.

3.1 Primary Objective

- To evaluate efficacy, as measured by overall response rate by investigator.

3.2 Secondary Objectives

- To evaluate efficacy, as measured by the following:
    - Duration of response as determined by investigator
    - Progression-free survival as determined by investigator
    - Overall survival
    - Rate of complete response or complete metabolic response as determined by investigator
    - Time to response as determined by investigator
- Safety and tolerability

3.3 Exploratory Objectives

[redacted]

4 STUDY ENDPOINTS

4.1 Primary Endpoint

- Overall response rate (ORR) measured by investigator

4.2 Secondary Endpoints

Efficacy:

- Duration of response as determined by investigator
- Progression-free survival (PFS) as determined by investigator

- Overall survival
- Rate of complete response (CR) or complete metabolic response (CMR) as determined by investigator
- Time to response as determined by investigator

Safety:

- Safety and tolerability of zanubrutinib in combination with rituximab as evaluated by the incidence and severity of adverse events (AEs), clinical laboratory abnormalities, deaths and cause of death

4.3 Exploratory Endpoints

[redacted]

5 SAMPLE SIZE CONSIDERATIONS

Total sample size for the study will be approximately 40 patients, 20 for each cohort. There is no pre-specified hypothesis for the study endpoints, thus the sample size is not based on the statistical power calculation.

6 STATISTICAL METHODS

6.1 Analysis Sets

The Safety Analysis Set includes all patients who received at least 1 dose of study drug (zanubrutinib or rituximab). The Safety Analysis Set will be used for all efficacy and safety analyses.

[redacted]

A summary of analysis sets for all patients will provide the number and percentage of patients in each analysis set.

6.2 Data Analysis General Considerations

6.2.1 Definitions and Computations

Study drug: Study drugs for this study are zanubrutinib and rituximab. Study treatment for this study is zanubrutinib in combination with rituximab.

Study day: Study day will be calculated in reference to the date of the first dose of any study drug. For assessments conducted on or after the date of the first dose of study drug, study day will be calculated as (assessment date – date of first dose of study drug + 1). For assessments conducted before the date of the first dose of study drug, study day is calculated as (assessment date – date of first dose of study drug). There is no study day 0.

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings. Study day and any corresponding durations will be presented based on the imputations specified in Appendix A.

Baseline: Unless otherwise specified, a baseline value is defined as the last non-missing value collected before the first dose of study drug.

All calculations and analyses will be conducted using SAS version 9.4 or higher.

6.2.2 Handling of Missing Data

Missing data will not be imputed unless otherwise specified elsewhere in the statistical analysis plan. Missing dates or partially missing dates will be imputed conservatively for prior/concomitant medications/procedures, diagnosis, prior therapy/response to prior therapy, subsequent anti-cancer therapies, adverse events and deaths as provided in Analysis Details Specification document for analyses that require the date values. Specific rules for handling of missing or partially missing dates for prior/concomitant medications/procedures, diagnosis, prior therapy/response to prior therapy, subsequent anti-cancer therapies, adverse events, and deaths are provided in Appendix A.

When summarizing categorical variables, patients with missing data are generally included in the denominator to calculate percentages unless otherwise specified. When needed, the category of "Missing" is created and the number of patients with missing data is presented.

When summarizing continuous variables, patients with missing data are not included in calculations unless otherwise specified.

No imputation of AE grades will be performed. Treatment-emergent adverse events (TEAEs) with missing Common Terminology Criteria for Adverse Events (CTCAE) grade will only be summarized in the all-grades column.

If the assessment of the relationship of an AE to study treatment is missing, then the AE is assumed to be related to the study treatment in the safety analysis summary. No imputation will be done in the AE listings.

By-visit summary of variables with missing data will use only non-missing data, not imputed one, unless otherwise specified. Unscheduled visits will not be included in by-visit summaries.

6.2.3 Adjustment for Covariates

Not applicable.

6.2.4 Multiplicity Adjustment

No formal hypothesis testing is planned for this study. Adjustment for multiplicity is not planned.

6.2.5 Data Integrity

Before any pre-specified statistical analysis begins, the integrity of the data should be reviewed to assure fit-for-purpose. The data set for analysis should be an accurate and complete representation of the patients' relevant outcomes from the clinical database. All essential data should be complete and reviewed up to database lock date. Critical consistency checks and appropriate source data verification should be complete according to the final data extraction plan.

6.3 Patient Characteristics

Patient characteristics will be summarized by disease type and overall based on safety analysis set, unless otherwise specified.

6.3.1 Patient Disposition

The following patient disposition information will be summarized for all enrolled patients:

- Number of patients enrolled
- Number of treated patients
- Number (%) of treated patients who discontinued study treatment
- Reason for study treatment discontinuation
- Number (%) of treated patients who discontinued study
- Reason for study discontinuation

The number (%) of patients still receiving treatment and still in the study at database lock will also be summarized.

Study follow-up time will be defined as the time from first dose date to the death date or end of study date (whichever occurs earlier) for patients discontinued from study, or the database cutoff date for ongoing patients. Study follow-up time will be estimated by median and range.

6.3.2 Protocol Deviations

Study conduct and protocol deviations will be monitored during this study by the clinical research organization (Parexel) and the sponsor (BeiGene). The clinical research organization will assess potential protocol deviations as minor or major according to the protocol deviation specification in this study and review them with BeiGene study team. The major protocol deviations are defined as those that are likely to have a major impact on the patient’s rights, safety, well-being, and/or on the validity of data for analysis. The final determination of important protocol deviations (culled

from the list of major protocol deviations) will be made by the BeiGene's medical team, using the criteria for important protocol deviation described in the ICH E3 guidelines before the database lock. Important protocol deviations will be summarized by deviation category. Listing will also be provided.

6.3.3 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics including the following will be summarized using descriptive statistics:

- Age (years) and age categorized (years) as <65, ≥65
- Sex
- Race
- Eastern cooperative oncology group performance status (categorical)
- Height (cm) and weight (kg)
- Body mass index (in kg/m^2)
- Body surface area (in m^2)
- Hepatitis B core antibody status

A listing of demographic and other baseline characteristics will be provided.

6.3.4 Disease History

Disease history and baseline disease characteristics including followings will be summarized by descriptive statistics:

- Time since initial diagnosis to first dose of study drug (months)
- Disease stage at study entry (I, II, II bulky, III, IV)
- International prognostic index (low, low intermediate, high intermediate, and high for non-GCB DLBCL and MZL patients) and FL international prognostic index (low, intermediate, and high for FL patients)
- Time from last disease progression to first dose of study drug (months)
- Bone Marrow Involvement (yes, no, indeterminate)
- Epstein–Barr virus-encoded RNA (positive, negative, not available)
- Hemoglobin
- Neutrophils
- Platelets
- Lactate dehydrogenase
- Prior transplant
- Prior radiotherapy

A listing of disease history and characteristics will be provided.

6.3.5 Prior Anticancer Drug Therapies

Prior therapy for lymphoma including following information will be summarized and listed:

- Number of prior lines of therapy
- Prior anticancer drug therapy and category
- Duration of last line therapy (months)
- Best response to last line therapy
- Time from end of last line therapy to first dose of study drug (months)

6.3.6 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary drug codes version Sep 2018 B3 or later and will be further classified to the appropriate anatomical therapeutic chemical code.

Prior medications are defined as medications that started before the first dose date. Concomitant medications are defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 days following last dose of zanubrutinib or 90 days following last dose of rituximab, whichever comes later; or initiation of a new anticancer therapy, if it occurs prior to the other two dates. For the purpose of determining if a medication should be noted as a concomitant medication, the imputation rules stated in Appendix A and Analysis Details Specification document will be used.

The number (%) of patients reporting prior medications and the number (%) of patients reporting concomitant medications will be summarized by anatomic therapeutic chemical medication class Level 2 and World Health Organization drug dictionary preferred name. A listing of prior and concomitant medications will be provided.

6.3.7 Medical History

Medical History will be coded using Medical Dictionary for Regulatory Activities (MedDRA) (version 18.1 or higher). The number (%) of patients reporting a history of any medical condition, as recorded on the electronic case report form, will be summarized by MedDRA system organ class (SOC) and preferred term (PT). A listing of medical history will be provided.

6.4 Efficacy Analysis

Response assessment for disease status-based efficacy endpoints (ORR, CR, CMR, time to response, duration of response and PFS) will be performed per the Lugano Classification (Cheson et al 2014).

The efficacy analysis will be performed by disease type separately. All efficacy analyses will be based on the Safety Analysis Set.

All efficacy endpoints based on Lugano Classification will be summarized based on the overall disease assessment results. Overall disease assessment will be based on positron emission tomography (PET) and computed tomography (CT) for Non-GCB DLBCL and FL patients, and will be based on CT for MZL patients. Besides, disease response will be summarized per CT-based assessment for Non-GCB DLBCL and FL patients.

6.4.1 Primary Efficacy Endpoint

Overall Response Rate by investigator

The primary endpoint of the study is ORR, defined as proportion of patients who achieved Best Overall Response (BOR) of partial response or higher.

A point estimate and a 2-sided 95% exact binomial confidence interval using Clopper-Pearson method will be provided for ORR.

A patient's BOR is the best response recorded from Cycle 1 Day 1 until database lock, progressive disease, or start of new anticancer treatment, whichever is the earliest. Responses recorded after initiation of new anticancer treatment will not be considered for best overall response. Response rate is a crude proportion of patients with best overall responses in corresponding response categories.

Patients without postbaseline tumor assessment will be considered as non-responders. The number and proportion of patients who achieved each BOR category will be calculated.

6.4.2 Secondary Efficacy Endpoints

6.4.2.1 Rate of complete response or complete metabolic response by investigator

Rate of CR or CMR is defined as the proportion of patients whose BOR met CR or CMR criteria among all patients in the safety analysis set.

Rate of CR or CMR will be analyzed using the same methods applied for ORR analysis. A point estimate and a 2-sided 95% exact binomial confidence interval using the Clopper-Pearson method will be provided for rate of CR or CMR.

6.4.2.2 Progression Free Survival by investigator

PFS is defined as the time (in months) from the first dose date of study drug to the date of progressive disease (PD) or death (due to any cause), whichever occurs first:

PFS = (The earlier of disease progression or death date – first dose date of study drug +1) / 30.4375.

PFS will be right-censored for patients who met one of the following conditions: 1) no baseline and/or postbaseline disease assessments; 2) starting a new anticancer therapy before PD or death; 3) death or PD immediately after more than 6 months since last disease assessment; and 4) alive without documentation of disease progression. For such patients, the primary analysis of PFS will be right-censored according to the convention described in Table 1 which is based on the Food and Drug Administration Guidance for Industry, "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" (2018) and references within the guidance document.

Only those procedures with valid assessment results will be used in determination of PFS.

Table 1 Date of Progression or Censoring for Progression-free Survival

Situation	Date of Progression Event or Censoring	Outcome
1. Death or PD between planned disease assessments	Date of death or first disease assessment showing PD, whichever occurs first	Event
2. Death before first PD assessment or between adequate assessment	Date of death	Event
3. No baseline and/or post-baseline disease assessments	Date of first dose	Censored
4. New anticancer treatment started before PD or death	Date of last disease assessment without PD prior to start of a new anticancer treatment	Censored
5. Death or PD immediately after more than 6 months after last disease assessment	Date of last disease assessment that is before death or PD	Censored
6. Alive and without PD	Date of last disease assessment	Censored

The distribution of PFS, including median and PFS rate at selected time points such as 6, 9, 12 and 15 months, will be estimated using the Kaplan-Meier method. The 95% confidence interval for median and other quartiles of PFS will be generated by using Brookmeyer method (Brookmeyer and Crowley 1982), whereas the 95% confidence interval for PFS rate at landmark time points will be generated by using Greenwood formula (Greenwood 1926). Median PFS follow-up time will be estimated by reverse Kaplan-Meier method (Schemper and Smith 1996). Kaplan-Meier curves for PFS will be also generated.

A listing will be provided for the information of patient PFS, date of progression or censoring, and reason.

6.4.2.3 Duration of response by investigator

Duration of response for overall responders is defined as the time (in months) from the date of first overall response (partial response or higher) to the date of PD or death for any cause (whichever occurs earlier). The analysis methods, including censoring rules, will be the same as those for PFS. Only overall responders will be included in the analysis.

6.4.2.4 Time to response by investigator

Time to response for overall responders is defined as time (in months) from the date of the first dose of study drug to the date of the first overall response. Time to response will be summarized by sample statistics such as mean, median and range for overall responders only.

6.4.2.5 Overall Survival

Overall survival is defined as the time (in months) from the date of first study dose to the date of death due to any cause. Patients who remained alive as of the database lock or discontinuation of the study (discontinued study due to reasons other than "Death") will be censored at the last date the patient was known to be alive on or before database lock. The analysis methods for overall survival will be the same as those for PFS.

6.4.3 Subgroup Analyses

Primary endpoint will be summarized by disease type in the following subgroups defined by baseline demographic and disease characteristics, as appropriate (i.e. when there is sufficient number of patients in the subgroup, otherwise relevant subgroups may be combined): sex, age group (< 65 vs. ≥ 65), eastern cooperative oncology group performance status (0 vs. ≥ 1), disease stage at study entry (I/II/II bulky vs. III/IV), International prognostic index (low vs low intermediate/high intermediate/high for non-GCB DLBCL and MZL patients; low vs intermediate/high for FL patients), number of prior lines of therapy (1 vs. ≥2). The aforementioned demographic and disease characteristics and their respective categories are subject to change, if warranted, to better represent the data. Subgroup analysis of ORR will be presented in forest plots.

6.5 Safety Analyses

All safety analyses will be based on the safety analysis set. Safety analysis will be summarized by disease type and overall, unless otherwise specified.

The study set up a SMC. The SMC monitors safety data according to the SMC charter (Appendix C) throughout the study.

6.5.1 Extent of Exposure

Extent of exposure to the zanubrutinib will be summarized descriptively with respect to the following:

- Number of cycles received: defined as duration of exposure (days)/28
- Duration of exposure (months): defined as the duration from the date of the first dose to the end of treatment decision date for patients discontinued zanubrutinib treatment, or the data cutoff date for ongoing patients.
- Number (%) of patients in each category of duration of exposure
- Cumulative dose administered (g): defined as the cumulative dose of zanubrutinib received during the treatment period

  Note: If the actual dose received during a period is unknown (e.g. diary not returned, and no other information can be used), it will be considered as the study drug was administered as prescribed conservatively.

- Actual dose intensity (mg/day): defined as the cumulative dose (in mg) received by a patient divided by the duration of treatment (in days), where duration of treatment is calculated as latest exposure record ending date - first dose date + 1.

  Note: For patients who are ongoing at the data cutoff, the actual dose intensity is calculated based on study drug administration records prior to data cutoff as the cumulative dose (in mg) received by a patient prior to the data cutoff divided by the duration from first dose date to the end date of the last zanubrutinib administration record.

- Relative dose intensity: defined as the ratio of the actual dose intensity (mg/day) to the planned dose intensity in percentage. Planned dose intensity is 320 mg/day.

- Number (%) of patients with dose reduction, drug interruption and dose missed/changed

- Number of dose reduction, drug interruption and dose missed/changed per patient

- Reasons for dose reduction, drug interruption, dose missed/changed

- Duration of drug interruption

- Cycle in which the first dose reduction/drug interruption occurred

Extent of exposure to the rituximab will be summarized descriptively with respect to the following:

- Duration of exposure (months): defined as the duration from the date of the first dose to the last dose date of rituximab.

- Number of doses received

- Number (%) of patients received rituximab treatment by time point

- Number (%) of patients with drug interruption, drug delay and dose missed

- Number of drug interruption per patient

- Reasons for drug interruption, drug delay and dose missed

- Cycle in which the first drug interruption occurred

For zanubrutinib, dose reduction is defined as any planned dose reduction from the original planned dose (160mg twice a day), regardless of reasons. Drug interruption is defined as any dose temporary discontinuation determined by investigator. Dose missed/changed is defined as any dose temporary discontinuation/change determined by the patient.

For rituximab, drug interruption is defined as any dose temporary discontinuation due to AE. Dose missed is defined as any dose temporary discontinuation due to reasons other than AE.

For patients with drug interruption due to AE but with missing start/end date, the end date will be imputed with the corresponding AE stop date, the dose interruption start date will be back calculated based on the dosage missing reported. If the dosage is also missing, the start and stop date of the drug interruption will be imputed with the AE start/stop date.

6.5.2 Adverse Events

Adverse Event

AEs will be graded by the investigators using NCI CTCAE v4.03. The AE verbatim descriptions (investigator reported terms from the case report form) will be classified into standardized medical terminology using the MedDRA. Adverse events will be coded to the MedDRA (Version 18.1 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary SOC are also captured in the database.

A treatment-emergent adverse event is defined as an adverse event that emerges during treatment, having been absent pretreatment, or worsens relative to the pretreatment state, starting on or after the first dose of study drug up to 30 days following discontinuation of zanubrutinib or 90 days following discontinuation of rituximab, whichever comes later; or initiation of new anticancer therapy, if it occurs prior to the other two dates. Worsening of an event to Grade 5 beyond day 30 after last dose of zanubrutinib or day 90 after last dose rituximab of a treatment-emergent adverse event is also considered a treatment-emergent adverse event. Only those AEs that were treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in patient data listings.
Treatment-related AEs include those events considered by the investigator to be related, possibly related, probably related, unlikely related to study drug, or with missing assessment of the causal relationship.

TEAE will be summarized based on the number (%) of patients experiencing events by MedDRA SOC and PT. A patient reporting the same AE more than once will be counted only once when calculating incidence 1) within a given SOC, and 2) within a given SOC and PT combination. For such cases, the maximum CTCAE toxicity grade and strongest causal relationship to study drug for the event will be used in the incidence calculations.

An overall summary of TEAEs will include the number (%) of patients:

- With at least one TEAE
- With at least one treatment-related (related to zanubrutinib and/or rituximab) TEAE
- With at least one Grade 3 or higher TEAE
- With at least one treatment-related (related to zanubrutinib and/or rituximab) TEAE of Grade 3 or higher
- With at least one TEAE leading to death
- With at least one treatment-related (related to zanubrutinib and/or rituximab) TEAE leading to death
- With at least one serious TEAE

- With at least one treatment-related (related to zanubrutinib and/or rituximab) serious TEAE
- With at least one TEAE leading to treatment discontinuation
- With at least one treatment-related (related to zanubrutinib and/or rituximab) TEAE leading to treatment discontinuation
- With at least one TEAE leading to dose modification (dose reduction/drug interruption) of zanubrutinib and/or rituximab
- With at least one treatment-related (related to zanubrutinib and/or rituximab) TEAE leading to dose modification (dose reduction/drug interruption) of zanubrutinib and/or rituximab
- With at least one TEAE leading to dose reduction of zanubrutinib (only for overall summary table)
- With at least one treatment-related (related to zanubrutinib and/or rituximab) TEAE leading to dose reduction of zanubrutinib (only for overall summary table)
- With at least one TEAE leading to drug interruption (only for overall summary table) of zanubrutinib and/or rituximab
- With at least one treatment-related (related to zanubrutinib and/or rituximab) TEAE leading to drug interruption (only for overall summary table) of zanubrutinib and/or rituximab
- With at least one TEAE of special interest TEAE
- With at least one treatment-related (related to zanubrutinib and/or rituximab) TEAE of special interest TEAE

Summaries of all above TEAEs will be provided by SOC and PT, unless otherwise specified.

Summaries of all TEAEs, serious adverse event, Grade 3 or higher TEAEs and treatment-related TEAEs will also be provided by PT only. Summaries of all TEAEs will be provided by SOC, PT, and worst grade.

In addition, summary of below TEAEs will be provided by SOC and PT for zanubrutinib and rituximab separately:

- With at least one treatment-related TEAE (zanubrutinib and rituximab-related separately)
- With at least one treatment-related Grade 3 or higher TEAE (zanubrutinib and rituximab-related respectively)
- With at least one treatment-related serious TEAE (zanubrutinib and rituximab-related separately)
- With at least one TEAE leading to zanubrutinib dose modification (dose reduction/drug interruption)
- With at least one TEAE leading to rituximab interruption

Adverse Event of Special Interest

AE of special interest (AESI) will be defined and summarized by AESI category name and PT for each of following groups:

- All AESIs
- Treatment-related AESIs (study treatment, zanubrutinib and rituximab related separately)
- AESI of Grade 3 or higher
- Serious AESIs
- AESIs leading to treatment discontinuation
- AESIs leading to dose modification (dose reduction/drug interruption) of any study drug and zanubrutinib separately, and leading to rituximab interruption
- AESIs leading to death

Summary of all AESIs will also be provided by worst grade. The AESI categories and detailed search criteria will be provided separately.

Summary will also be provided for TEAEs related to liver, arrhythmia and diarrhea.

Exposure-Adjusted Incidence Rates

Exposure-adjusted incidence rate by category will also be calculated for AESIs. In calculating exposure-adjusted incidence rate, the analysis restricts on the occurrence of the first event per patient and ignores the existence of later (multiple) events as these cannot be assumed to occur independent of previous events. The incidence rate for a patient is derived from the duration of treatment exposure of that patient. A patient's duration of exposure is given either 1) by the time when the first event has occurred, or the treatment had ended, whichever is earlier (non-censored data), or 2) by the total duration of exposure from first dose date to end of treatment date or the data cutoff date (whichever is earlier) in case the patient does not experience the event (censored data). Depending on whether a patient has an event or not, the duration of exposure enters the denominator in its non-censored or censored form, respectively. The exposure-adjusted incidence rate per event considers the first event per patient only, and the corresponding exposure time in the denominator:

$$EAIR_{event} = \frac{\sum_{i=1}^{n} AESI_{event,i}}{\sum_{i=1}^{n} t_{event,i}}$$

Whereby $AESI_{event,i}$ represents if patient i experienced the event (1) or not (0), and $t_{event,i}$ as time when the first AESI occurs or the treatment ends, whichever is earlier (non-censored data) or total duration of exposure if no event occurs (censored data).

A summary of the number of deaths and the cause of death, classified by deaths within 30 days of last dose of zanubrutinib or 90 days of last dose of rituximab (whichever is later) and deaths more than 30 days after last dose of zanubrutinib or 90 days of last dose of rituximab (whichever is later), will be provided.

Patient data listings of deaths, all AEs, serious adverse events, treatment-related AEs, AEs of Grade 3 or higher, AEs that led to death, AEs that led to dose modification (reduction/interruption), AEs that led to treatment discontinuation, and AESIs will be provided.

Other exploratory analysis may be performed if deemed necessary.

6.5.3 Laboratory Values

All hematology, serum chemistry, coagulation, and urinalysis results for each patient will be presented in data listings. Actual value and change from baseline for all hematology, serum chemistry, and coagulation parameters will be summarized at each scheduled visit.

Selected laboratory test results will be assigned toxicity grades using NCI CTCAE 4.03 for all patients. These laboratory parameters of interest are:

Hematology	**Serum Chemistry**		**Coagulation***
Hemoglobin (decrease)	Alanine transaminase (increase)	Albumin (decrease)	Activated partial thromboplastin time (increase)
Platelets (decrease)	Aspartate transaminase (increase)	Sodium (increase, decrease)	International Normalized Ratio (increase)
White blood cell (increase, decrease)	Alkaline Phosphatase (increase)	Phosphorus (decrease)	
Absolute Neutrophil Count (decrease)	Total Bilirubin (increase)	Potassium (increase, decrease)	
Absolute Lymphocyte Count (increase, decrease)	Creatinine (increase)	Magnesium (increase, decrease)	
	Calcium (increase, decrease)		
	Glucose (increase, decrease)		

* Coagulation parameters may not be summarized if only few patients have post-baseline assessments.

For hypocalcemia and hypercalcemia, serum calcium will be corrected using the formula:

> Corrected calcium = Serum calcium + 0.8 * (4 – serum albumin) where serum calcium is recorded in mg/dL and serum albumin is recorded in g/dL.

Shift tables assessing the toxicity grade at baseline versus worst toxicity recorded post-baseline will be presented. A summary of the number (%) of patients with Grade 3 or higher toxicity at postbaseline and change of more than 2 grades from baseline will be provided separately for selected laboratory parameter of interest. In the summary of laboratory parameters by CTCAE toxicity grade, parameters with CTCAE toxicity grading in both high and low directions will be summarized separately.

Summary of urinalysis (dipstick) will be summarized at each scheduled visit.

Listing of Grade 3 or higher laboratory values will also be provided. Box-whisker plots will be generated for parameters of interest.

Hy's Law criteria is defined with alanine aminotransferase or aspartate aminotransferase > 3xULN and total bilirubin > 2xULN and alkaline phosphatase < 2xULN; total bilirubin and alkaline phosphatase were both within 28 days after alanine aminotransferase or aspartate aminotransferase elevation. Incidence of patients who met one or more of the Hy's law criteria will be summarized. A listing of patients with alanine aminotransferase / aspartate aminotransferase > 3x ULN and total bilirubin > 2x ULN will be generated.

6.5.4 Vital Signs

Actual value and change from baseline for all vital signs and weight will be summarized at each scheduled visit.

Shift tables assessing the toxicity grade at baseline versus worst toxicity recorded post-baseline for systolic and diastolic blood pressure will be presented. Box-whisker plots will be generated for actual value and change from baseline for systolic and diastolic blood pressure.

Vital signs will be listed by patients and visits.

6.5.5 Physical Examination

Physical examination results will be listed without summary.

6.5.6 Electrocardiograms

Electrocardiogram assessments will be performed at the screening, cycle 1 and safety follow-up visits. Patient listing for electrocardiogram data will be provided.

6.5.7 Eastern Cooperative Oncology Group

Eastern cooperative oncology group performance status will be summarized and listed at each visit. Shift table assessing the eastern cooperative oncology group performance status at baseline versus worst performance status post-baseline will be presented.

6.5.8 Other Safety Endpoints

Pregnancy test and viral serology will be listed.

6.6 Pharmacokinetics analyses

[redacted]

6.7 Biomarker/Pharmacodynamic Analyses

[redacted]

6.8 Other Analyses

Additional exploratory analyses may be conducted as appropriate. Any exploratory analyses that are performed will be appropriately titled/labeled as exploratory and will be clearly distinguished from planned analyses when results are reported in the Clinical Study Report.

7 INTERIM ANALYSIS

No interim analysis is planned for this study.

8 CHANGES IN THE PLANNED ANALYSIS

Changes made to the planned analysis are as follows:

- The PK Analysis Set definition was updated to provide more clarity.

9 REFERENCES

1. Brookmeyer, R. and Crowley, J. (1982) *A confidence interval for the median survival time*. Biometrics, 38, 29-41.
2. Cheson, BD et al. (2014) *Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano Classification*. J Clin Oncol, 32(27):3059–3068.
3. Food and Drug Administration Center for Drug Evaluation Research (CDER) and Center for Biologics Evaluation and Research (CBER) (2018). *FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics*. https://www.fda.gov/media/71195/download
4. Greenwood, M. (1926) *The natural duration of cancer. Public health and medical patients*, 33: 126.

5. Schemper, M, and Smith, T.L. (1996) *A note on quantifying follow-up in studies of failure time*. Controlled Clinical Trials, 17:343-346

10 APPENDIX

Appendix A: Missing Data Imputation Rule

In general, missing or partial dates will not be imputed at data level. The following rules will apply for the specific analysis and summary purposes mentioned below only.

A.1 Prior/Concomitant Medications/Procedures

When the start date or end date of a medication is partially missing, the date will be imputed to determine whether the medication is prior or concomitant. The following rules will be applied to impute partial dates for medications:

If start date of a medication is partially missing, impute as follows:

- If both month and day are missing, then set to January 01
- If only day is missing, then set to the first day of the month

If end date of a medication is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month

If start date or end date of a medication is completely missing, do not impute.

If the imputed end date > death date/last known alive date or end of study date, then set to the death date/last known alive date or end of study date, whichever occurs first.

A.2 Adverse Events

The imputation rule for the safety analyses will be used to address the issues with partial dates. When the start date or end date of an adverse event is partially missing, the date will be imputed to determine whether the adverse event is treatment-emergent. When in doubt, the adverse event will be considered treatment emergent by default. The following rules will be applied to impute partial dates for adverse events:

If start date of an adverse event is partially missing, impute as follows:

- If both month and day are missing, then the imputed day and month will be January 01 or the first dosing date if they have the same year, whichever is later.
- If only day is missing, then the imputed day will be the first day of the month or the first dosing date if they have the same month and year, whichever is later
- If start date is completely missing, the imputed day will be the first dosing date as long as AE end date is not before the first dosing date.

If end date of an AE is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month
- If end date is completely missing, do not impute.

If the imputed AE end date > death date/last known alive date or end of study date, then set to the death date/last known alive date or end of study date, whichever occurs first.

A.3 Deaths

In case complete death dates are not recorded, impute as follows:

- If both month and day are missing, then the imputed month and day will be January 01 or the last date of patient known to be alive + 1, whichever is later.
- If only day is missing, the death will be assumed to be on the first day of the month or the last date of patient known to be alive +1, whichever is later.

A.4 Subsequent Anti-cancer Therapies

If the start date of a subsequent anti-cancer therapy is incomplete or missing, impute as follows:

- If both month and day are missing, then the imputed month and day will be January 01 or the last day of the month for the last adequate disease assessment if they have the same year.
- If only day is missing, then the imputed day will be the first day of the month.

A.5 Diagnosis

If a diagnosis date is partially missing, impute as follows:

- If both month and day are missing, then set to January 01
- If only day is missing, then set to the first day of the month

If a diagnosis date is completely missing, do not impute.

A.6 Prior Therapy/Response to Prior Therapy

If a prior therapy or response to prior therapy date is partially missing, impute as follows:

- If only day is missing, then set to the 15th of the month or the first study drug dose date-1, whichever is earlier. An imputed start date can be no later than the end date and vice versa.

No imputation will be performed for all other types of missing dates

Appendix B: The International Prognostic Index

B1. Follicular Lymphoma International Prognostic Index

The FL international prognostic index uses five independent predictors of inferior survival:

- age >60 years
- hemoglobin <12 g/dL
- serum lactate dehydrogenase >normal
- Ann Arbor stage III/IV
- number of involved nodal areas > 4

The presence of 0-1, 2, and ≥3 adverse factors defines low, intermediate, and high-risk disease, respectively.

B.2 International Prognostic Index for DLBCL and MZL

- age >60 years
- serum lactate dehydrogenase >normal
- Performance status 2-4
- Stage III or IV
- Extranodal involvement >1 site

The presence of 0-1, 2, 3, and 4-5 adverse factors defines low, low intermediate, high intermediate and high-risk disease, respectively.

Appendix C: Safety Monitoring Committee Charter

The safety monitoring committee charter is provided in a separate document.