16.1.9 DOCUMENTATION OF STATISTICAL METHODS

STATISTICAL ANALYSIS PLAN

Study Protocol Number:	BGB-3111-218
Study Protocol Title:	A Phase 2, Single-Arm, Open-Label, Multicenter Study of the Bruton Tyrosine Kinase Inhibitor Zanubrutinib in Patients With CD79B Mutant Relapsed/Refractory Diffuse Large B-Cell Lymphoma
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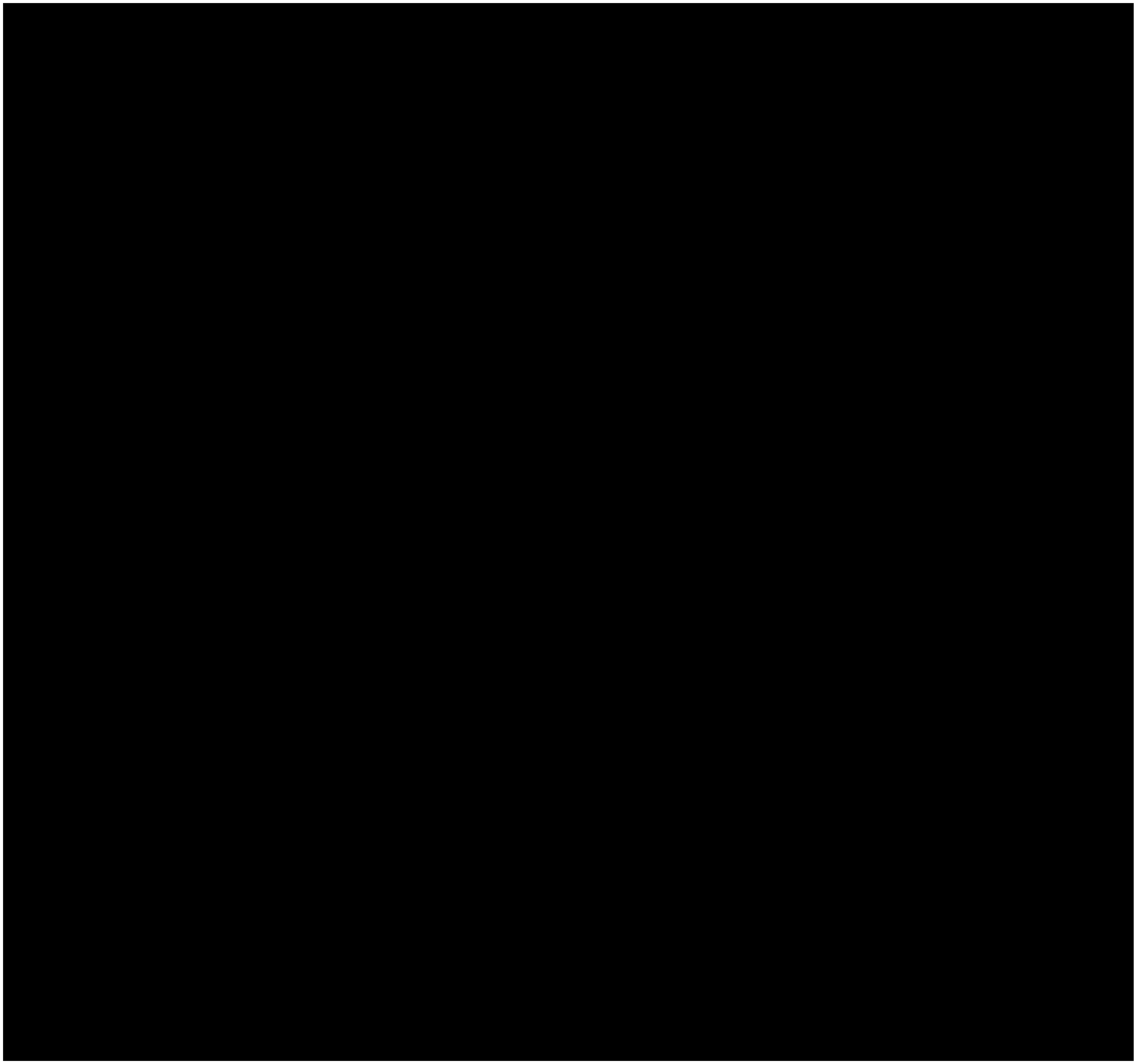

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AEs	Adverse events
ADI	Actual dose intensity
AUC	Area under the plasma concentration-time curve
BID	Bis in die (twice a day)
BMI	Body mass index
BTK	Bruton tyrosine kinase
CI	Confidence interval
C_{max}	Maximum observed plasma concentration
CR	Complete response
CT	Computed tomography
DIPP	Data integrity protection plan
DOR	Duration of response
eCRF	Electronic case report form
EAIR	Exposure-Adjusted Incidence Rate
ECOG	Eastern Cooperative Oncology Group

EDC	Electronic data capture
FDA	Food and Drug Administration
FDG	[18F]fluorodeoxyglucose
FL	Follicular lymphoma
GHS/QoL	Global health status/Quality of life
ICR	Independent central review
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
NHL	Non-Hodgkin's lymphoma
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial response

PT	Preferred term
QD	Quaque die (once a day)
RDI	Relative dose intensity
SAEs	Serious adverse events
SMQ	Standardized MedDRA Query
sNDA	Supplemental new drug application
SOC	System organ class
TEAE	Treatment-emergent adverse event
WHO DD	World Health Organization Drug Dictionary

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report the results for BGB-3111-218: A Phase 2, Single-Arm, Open-Label, Multicenter Study of the Bruton Tyrosine Kinase Inhibitor Zanubrutinib in Patients With CD79B Mutant Relapsed/Refractory Diffuse Large B-Cell Lymphoma. The focus of this SAP is the planned Primary Analysis specified in this study protocol. Details of the pharmacokinetic/pharmacogenomics analyses are not described in this SAP.

2 STUDY OVERVIEW

This single-arm, open-label, multicenter Phase 2 study is designed to assess the efficacy and safety of zanubrutinib in patients with CD79B mutant R/R DLBCL. The primary efficacy endpoint is the overall response rate determined by the investigator assessment. Disease response will be assessed per the Lugano classification (Cheson et al 2014). The primary analysis will take place approximately 6 months after the first dose of the last patient

The treatment period starts with the first day of zanubrutinib administration and continues until the last dose of zanubrutinib has been administered. Zanubrutinib will be administered orally as two 80-mg capsules twice a day (160 mg twice a day) continuously. Each cycle is 28 days in length. Patients will receive zanubrutinib until disease progression, unacceptable toxicity, loss to follow-up, or the end of the study, whichever occurs first.

Response will be evaluated on the basis of clinical and radiologic evaluations using the Lugano classification. All patients must have a baseline PET-CT and CT scan with contrast of the chest, abdomen, pelvis, and neck if clinically indicated within 21 days before the first dose of study drug. PET-CT scans are required at screening, at Week 12 and Week 24 after treatment, and at the time when complete response (CR) or progressive disease (PD) is suspected. For fluorodeoxyglucose (FDG) non-avid disease, only CT scans will be required for post-baseline visit. Contrast CT will be performed at screening, every 12 weeks for 24 months, and every 24 weeks thereafter until disease progression, start of alternative anticancer therapy, loss to follow-up, or the end of the study, whichever occurs first. PET-CT may be used in lieu of a CT with contrast only if the CT of the PET-CT has been performed with diagnostic quality and contrast is administered. When both PET-CT and CT evaluations are available for the same tumor assessment visit, the results of

PET-CT shall prevail. Bone marrow biopsy and aspirate are required to assess bone marrow involvement of lymphoma for all patients during the screening period, unless they have been performed within 60 days before the first dose of study drug as part of the standard care and there has been no intervening therapy from the time of the biopsy/aspirate until the start of study drug. For patients with bone marrow involvement of lymphoma at baseline, repeated bone marrow biopsy and aspirate are required if CR is suspected. Clinical suspicion of disease progression at any time will require radiologic confirmation to be performed promptly, rather than waiting for the next scheduled radiologic assessment. Magnetic resonance imaging (MRI) and a non-contrast chest CT scan may be used instead of contrast CT for patients with serious contrast allergy; whichever method is used should be used consistently.

Assessments of safety will include AEs, SAEs, clinical laboratory tests, physical examinations, and vital signs. AEs will be graded for severity per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0.

3 STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVES:

- To evaluate the efficacy of zanubrutinib in patients with CD79B mutant relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL), as measured by overall response rate determined by the investigator assessment in accordance with the 2014 modification of the International Working Group on non-Hodgkin lymphoma (NHL) Criteria (hereafter referred to as the Lugano classification) (Cheson et al 2014).

3.2 SECONDARY OBJECTIVES:

- To evaluate the efficacy of zanubrutinib in patients with CD79B mutant R/R DLBCL, as measured by the following:
  - Complete response rate determined by investigator assessment
  - Duration of response determined by investigator assessment
  - Progression-free survival determined by investigator assessment
  - Time to response determined by investigator assessment
  - Overall survival

- To evaluate the safety and tolerability of zanubrutinib in patients with CD79B mutant R/R DLBCL when given as monotherapy

3.3 EXPLORATORY OBJECTIVES:

- To evaluate the pharmacokinetics (PK) of zanubrutinib in patients with CD79B mutant R/R DLBCL
- Summary of plasma concentrations of zanubrutinib
- To evaluate the correlation of clinical/genetic risk factors and clinical outcomes
- To explore mechanisms of disease resistance

4 STUDY ENDPOINTS

All the responses in the efficacy endpoints below are determined by investigator assessment according to the Lugano classification for NHL (Cheson et al 2014).

4.1 PRIMARY ENDPOINTS

- Overall response rate (ORR) determined by the investigator assessment.

4.2 SECONDARY ENDPOINTS

- Efficacy endpoints of zanubrutinib therapy are as follows:
    - Complete response rate determined by investigator assessment
    - Duration of response determined by investigator assessment
    - Progression-free survival determined by investigator assessment
    - Time to response determined by investigator assessment
    - Overall survival
- Safety parameters, including adverse events and serious adverse events (per NCI-CTCAE

Version 5.0), clinical laboratory measurements, physical examination, and vital signs

4.3 EXPLORATORY ENDPOINT

- PK evaluations of zanubrutinib, including summary of plasma concentrations
- Clinical outcomes (eg, overall response rate, complete response rate, duration of response, progression-free survival, time to response, and overall survival) by clinical/genetic risk factors
- Potential resistance biomarkers and mechanisms of disease resistance

5 SAMPLE SIZE CONSIDERATIONS

The sample size of the study is planned based on the level of precision of overall response rate estimate as well as the power of a hypothesis testing against a historical rate. The targeted overall response rate in this study is 50%, which is deemed a clinically meaningful improvement based on a historical control of 30%. Assuming a true overall response rate of 50% in the study population, 66 patients will provide 90% power to reject the null hypothesis of 30% ORR at the one-sided significance level of 0.025. The 95% Clopper-Pearson CI will be (37.4%, 62.6%) with a sample size of 66 patients, when the observed overall response rate is 50%. The historical control rate is obtained from referenced studies (Advani et al 2017; Assouline et al 2016; Budde et al 2018; Coiffier et al 2016; Czuczman et al 2017; Jurczak et al 2018; Hutchings et al 2018; Lesokhin et al 2016; Kalakonda et al 2020).

6 STATISTICAL METHODS

6.1 ANALYSIS SETS

Safety Analysis Set: includes all patients who receive at least one dose of zanubrutinib. The Safety Analysis Set will be used for both safety and efficacy analyses.

PK Analysis Set: includes all patients for whom there is at least one available postdose zanubrutinib PK concentration measurement.

6.2 DATA ANALYSIS GENERAL CONSIDERATIONS

6.2.1 Definitions and Computations

Study Treatment (study drug): The study drug is zanubrutinib monotherapy.

Study Day: Study Day will be calculated in reference to the date of first dose of study drug (Study Day 1). For assessments conducted on or after Study Day 1, Study Day will be calculated as (assessment date – Study Day 1 + 1). For assessments conducted before Study Day 1, Study Day will be calculated as (assessment date – Study Day 1). 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 the Appendix A.

Treatment duration: Treatment duration will be calculated as (date of last dose of study treatment – Study Day 1 + 1).

Baseline: Unless otherwise specified, a baseline value is defined as the last non-missing value collected before the first dose of study drug. Note that assessments that occur on the day of the first dose of study drug but prior to the time of the first dose can qualify to be a baseline value.

Post-baseline: A post-baseline value or assessment is defined as a value or assessment after 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 SAP. Missing dates or partially missing dates will be imputed conservatively for adverse events (AEs) and prior/concomitant medications/procedures. Specific rules for handling missing or partially missing dates for diagnosis, progression/relapse to prior therapy, AEs, and prior/concomitant medications/procedures are provided in the 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 the calculations unless otherwise specified.

By-visit endpoints will be analyzed using observed data unless otherwise specified. For observed data analyses, missing data will not be imputed, and only the observed records will be included.

6.2.3 Multiplicity Adjustment

Not applicable.

6.2.4 Data Integrity

Before 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 a pre-specified cutoff date. Critical consistency checks and appropriate source data verification should be completed according to the final data extraction plan.

6.3 PATIENT CHARACTERISTICS

6.3.1 Patient Disposition

The number (%) of patients screened, treated, discontinued from treatment with reasons, remained on treatment, completed treatment, discontinued from study with reasons, remained on study, completed study, and the duration of study follow-up will be summarized in the Safety Analysis Set.

6.3.2 Protocol Deviations

Patients with important protocol deviations will be identified and documented. Important protocol deviations will be summarized by category for all patients in the Safety Analysis Set. A listing of important protocol deviations will also be provided.

6.3.3 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized in the Safety Analysis Set including the following variables.

- Age (years) and age group (< 60 vs ≥ 60, < 65 vs ≥ 65 and < 75 vs ≥ 75)
- Sex

- Race and Ethnicity
- Weight and body mass index (BMI, kg/m^2)
- Eastern Cooperative Oncology Group (ECOG) performance status (0, 1, 2)

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

6.3.4 Disease History

The number (%) of patients reporting a history of disease and characteristics, as recorded on the eCRF, will be summarized in the Safety Analysis Set. Disease characteristics include the following variables:

- Time since initial diagnosis to first dose (months)
- Disease status at study entry (relapsed, refractory)
- Disease stage at study entry for DLBCL (stage I, II, II Bulky, III, IV)
- DLBCL IHC Subtype (GCB, non-GCB, unknown)
- DLBCL GEP Subtype (GCB, ABC, unclassified, unknown)
- Number of Extra Nodal Sites >1 (Yes, No)
- Baseline bone marrow involvement (aspirate) (yes, no, missing, indeterminate)
- B-Symptoms (yes, no, missing/unknown)
- Gene expression (IHC) (double expressor: expression of c-MYC+BCL2 or c-MYC+BCL2 or c-MYC+BCL6; triple expressor: expression of c-MYC+BCL2+BCL6)
- Gene rearrangement (FISH) (double hit: rearrangement of c-MYC+BCL2 or c-MYC+BCL6; triple hit: rearrangement of c-MYC+BCL2+BCL6)
- CD79B mutant status (central lab) (positive, negative)

6.3.5 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) (version 27.0). The number (%) of patients reporting a history of any medical condition, as recorded on the eCRF, will be summarized by system organ class (SOC) and preferred term (PT).

6.3.6 Prior Systemic Therapies

The following information related to prior therapy for DLBCL will be summarized by Anatomical Therapeutic Chemical (ATC) medication class Level 2 and World Health Organization Drug Dictionary (WHO DD) drug codes (version March 2024 or later) preferred name:

- Number of regimens of prior anticancer drug therapies
- Number of prior lines
- Prior BTK inhibitor treatment (yes, no)
- Prior CD20 treatment (yes, no)
- Prior alkylating agent treatment (yes, no)
- Reason(s) for discontinuation of last anticancer drug therapy (treatment completed, progressive disease, toxicity, other)
- Best response to the last anticancer drug therapy (complete response, partial response, stable disease, progressive disease, not evaluable, unknown)
- Time from the end of the last line of prior anticancer therapy to first dose date (months)
- Time from last disease progression to first dose date (months)
- Prior anticancer radiotherapy (yes, no)

6.3.7 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHO DD drug codes (version March 2024 or later) and will be further classified to the appropriate Anatomical Therapeutic Chemical (ATC) code.

Prior medications are defined as medications that started before the first dose date of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study treatment and were continuing at the time of the first dose of study treatment, or (2) started on or after the date of the first dose of study treatment up to 30 days after the last dose of zanubrutinib or initiation of a new anticancer therapy. For the purpose of determining if a medication should be noted as a concomitant medication, the imputation rules stated in Appendix A will be used.

The number (%) of patients reporting prior medications and concomitant medications will be summarized by ATC medication class Level 2 and WHO DD preferred name.

6.4 EFFICACY ANALYSIS

Efficacy assessments will use the Lugano Classification to assess overall disease response. All efficacy analyses will be performed using the Safety Analysis Set.

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the overall response rate determined by the investigator assessment, where the overall response rate is defined as the proportion of patients in the Safety Analysis Set whose best overall response is either CR or PR, and the best overall response is defined as the best response recorded from the start of zanubrutinib until the data cutoff date or the start of alternative anticancer treatment. Patients who drop out earlier with no post-baseline response assessment (for any reason) will be considered nonresponders for best overall response.

The overall response rate of historical control in this study is 30% based on the reported overall response rate in the literatures. Hence, the null and alternative hypotheses are set as follows:

H_0: Overall response rate = 30%

H_a: Overall response rate > 30%

A binomial exact test will be performed for hypothesis testing H_0 versus H_a in the Safety Analysis Set, and the overall type I error rate will be controlled at 1-sided significance level of 0.025. The primary analysis will take place approximately 6 months after the first dose of the last patient. If the null hypothesis can be rejected in primary analysis at significance level of 0.025, it will be concluded that the historical control of 30% can be ruled out. A 2-sided Clopper-Pearson 95% CI of the overall response rate will also be calculated to assess the precision of the estimation.

6.4.2 Secondary Efficacy Endpoints

6.4.2.1 Complete Response Rate by Investigator Assessment

The complete response rate will be determined by the investigator, and it is defined as the proportion of patients in the Safety Analysis Set whose best overall response is CR. The complete response rates along with their 95% CIs, using Clopper-Pearson method, will be provided.

6.4.2.2 Duration of Response by Investigator Assessment

The duration of response is defined as the time from the date that the response criteria are first met to the date that PD is objectively documented or death, whichever occurs first. The duration of response will be only summarized for responders. Censoring rules for duration of response followed progression-free survival censoring rules. The Kaplan-Meier method will be used to estimate duration of response curves and corresponding quartiles (including the median). A 2-sided 95% CI of all quartiles, if estimable, will be constructed with a generalized Brookmeyer and Crowley method (Brookmeyer and Crowley 1982). The duration of response event-free rates at 6, 12, and 18 months will be estimated using the Kaplan-Meier method along with the corresponding 95% CI constructed using Greenwood's formula (Greenwood 1926).

6.4.2.3 Progression-Free Survival by Investigator Assessment

Progression-free survival is defined as the time from the starting date of the therapy to the date of first documentation of disease progression or death, whichever occurs first. Patients who do not have disease progression will be censored at their last valid response assessment.

PFS will be right-censored according to the convention described in Table 1. The censoring rule is based on the FDA Guidance for Industry, 'Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics' (2015, Table C1, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-trial-endpoints-approval-non-small-cell-lung-cancer-drugs-and-biologics).

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

Situation	Date of Progression Event	Outcome
Death or PD between 2 planned disease assessments	Date of death or PD, whichever occurs first	Event
Death before the first disease assessment	Date of death	Event
Alive without baseline or post-baseline disease assessment	Date of first dose	Censored
Start new anticancer treatment before documented PD or death	Date of last disease assessment prior to the date of new anticancer treatment	Censored

PD or death after missing ≥ 2 consecutive planned disease assessments	Date of last disease assessment before death or PD; Use date of first dose if no assessment was performed before death or PD.	Censored
Alive without documented PD	Date of last disease assessment	Censored
Lost to follow-up* without documented PD or death	Date of last disease assessment	Censored

*This includes the consent withdrawal.

The progression-free survival will be analyzed for all patients in the Safety Analysis Set in a similar fashion as duration of response. The Kaplan-Meier method will be used to estimate progression event-free curves and corresponding quartiles (including the median). A 2-sided 95% CI of all quartiles, if estimable, will be constructed with a generalized Brookmeyer and Crowley method (Brookmeyer and Crowley 1982). The progression-free survival probability at 6, 12, and 18 months, defined as the percentages of patients in the Safety Analysis Set who remain alive and progression-free at the specified timepoints, will be estimated using the Kaplan-Meier method along with the corresponding 95% CI constructed using Greenwood's formula (Greenwood 1926).

6.4.2.4 Time to Response by Investigator Assessment

Time to response for responders is defined as the time from the first dose date to the date of the earliest qualifying response. Time to response will be summarized by descriptive statistics only.

6.4.2.5 Overall Survival

Overall survival is defined as the time from the starting date of the therapy to the date of death due to any reason. Patients who are known to be alive as of their last known status will be censored at their date of last contact. The overall survival will be analyzed similarly as progression-free survival.

6.4.3 Sensitivity Analysis

Not applicable.

6.4.4 Subgroup Analyses

The primary and selected secondary endpoints will be summarized by the DLBCL IHC subgroups. The subgroup variables and the cutoff values are subject to change if warranted to better represent the data.

6.4.5 Exploratory Efficacy Endpoints

The biomarker-related efficacy analysis will be provided in a separate report.

6.5 SAFETY ANALYSES

All safety analyses will be performed by treatment arms based on the Safety Analysis Set. Safety and tolerability will be assessed, where applicable, by incidence, severity, and change from baseline values for all relevant parameters including AEs, laboratory values, vital signs, and physical examination.

6.5.1 Extent of Exposure

The following measures of the extent of study drug exposure will be summarized:

- Duration of study treatment exposure (in months)
- Number (%) of treatment cycles
- Total dose (mg) received
- Actual dose intensity (ADI, mg/day) and relative dose intensity (RDI, %)

Duration of exposure in months is defined as (the last zanubrutinib administration date – the first zanubrutinib administration date + 1)/30.4375.

Number of treatment cycles is defined as duration of treatment (days) divided by 28.

The ADI is defined as the cumulative dose (mg) of zanubrutinib divided by the duration of zanubrutinib (day), which is defined as the last zanubrutinib administration date – the first zanubrutinib administration date + 1.

The RDI is defined as the ratio of ADI (mg/day) of zanubrutinib and the planned dose intensity (PDI, mg/day) of zanubrutinib, which is 320 mg/day.

6.5.2 Adverse Events

AEs will be graded by the investigators using CTCAE v5.0. The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be coded to the MedDRA (version 27.0) lower level term closest to the verbatim term. The linked MedDRA PT and primary SOC are also classified in the database.

A treatment-emergent adverse event is defined as an adverse event that had an onset date or worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to 30 days after the last dose of zanubrutinib, or the initiation of any alternative anticancer therapy, whichever comes first. Worsening of a treatment-emergent adverse event to Grade 5 beyond Day 30 after last dose of study drug or initiation of any alternative anticancer therapy is also considered a treatment-emergent adverse event. Treatment related adverse events include those adverse events considered by the investigator to be related to study drug or with missing assessment of the causal relationship.

An AE overview table, including the number of patients with TEAEs, treatment-emergent serious AEs (SAEs), TEAEs with Grade 3 or above, TEAEs that led to death, TEAEs that led to treatment discontinuation, TEAEs that led to dose modification (reduction, interruption, delay), treatment-related TEAEs, TEAEs of special interest (TE AESIs), Grade 3 or above TE AESIs, and serious TE AESIs will be provided.

Treatment-related AEs include those events considered by the investigator to be related, possibly or probably related to study drug or with a missing assessment of the causal relationship.

The incidence of TEAEs will be reported as the number (%) of patients with TEAEs by SOC, PT and the worst grade. A patient will be counted only once by the highest severity grade within an SOC and PT, even if the patient experienced more than 1 TEAE within a specific SOC and PT.

Summaries of TEAEs by SOC and PT will be presented for the following categories:

- Any TEAE
- Any Grade 3 or higher TEAE
- Any treatment-related TEAE

- Any treatment-related Grade 3 or higher TEAE
- Any serious TEAE
- Any treatment-related serious TEAE
- Any TEAE leading to treatment modification
- Any TEAE leading to dose reduction
- Any TEAE leading to dose interruption
- Any TEAE leading to dose discontinuation
- Any TEAE leading to death
- Any treatment-related TEAE leading to death
- Any treatment-related TEAE leading to treatment modification
- Any treatment-related TEAE leading to dose reduction
- Any treatment-related TEAE leading to dose interruption
- Any treatment-related TEAE leading to dose discontinuation

Moreover, all the summaries above will also be provided by PT only and by SOC, PT and maximum severity.

Incidence of TEAEs of special interest by category and PT will be presented for the following categories:

- Any TEAE of special interest
- Any Grade 3 or higher TEAE of special interest
- Any serious TEAE of special interest
- Any TEAE of special interest leading to dose reduction
- Any TEAE of special interest leading to dose interruption
- Any TEAE of special interest leading to dose discontinuation

The categories and detailed search criteria for TEAEs of special interest are described in Appendix B.

Time to the first TEAE of special interest along with the cumulative event rate and monthly hazard rate will be provided.

An overall summary of death and cause of death will be presented for the following categories:

- Total deaths
- Deaths within 30 days of last dose of study drug
- Deaths more than 30 days of last dose of study drug

Listings of all AEs, SAEs, AEs leading to dose reduction, AEs leading to dose interruption, AEs leading to dose delay, AEs leading to dose discontinuation, and all deaths will be provided.

6.5.3 Laboratory Values

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

The laboratory parameters of special interest for these summaries are:

Hematology	Serum Chemistry		Coagulation
Hemoglobin (decrease)	Alanine transaminase (ALT) (increase)	Albumin (decrease)	Activated partial thromboplastin time (aPTT) (increase)
Platelets (decrease)	Aspartate transaminase (AST) (increase)	Uric Acid (increase)	International Normalized Ratio (INR) (increase)
WBC (increase, decrease)	Alkaline Phosphatase (increase)	Sodium (increase, decrease)	
Absolute Neutrophil Count (ANC, decrease)	Total Bilirubin (increase)	Phosphorus (decrease)	

Absolute Lymphocyte Count (increase, decrease)	Creatinine (increase)	Potassium (increase, decrease)	
	Calcium (increase, decrease)	Magnesium (increase, decrease)	
	Glucose (increase, decrease)		

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.

Descriptive summary statistics (n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) for laboratory parameters and their changes from baseline will be summarized by visit.

Laboratory parameters that are graded in NCI-CTCAE Version 5.0 will be summarized by CTCAE grade. In the summary of laboratory parameters by CTCAE grade, parameters with CTCAE grading in both high and low directions (eg, calcium, glucose, magnesium, potassium, sodium) will be summarized separately.

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 will be provided for each laboratory parameter of interest. A listing of all Grade 3 or higher laboratory values will be provided. Box-whisker plots may be generated for parameters of interest.

Incidence of patients who met one or more of the Hy's Law criteria will be summarized. The Hy's Law criteria include ALT or AST > 3-fold ULN, total bilirubin > 2-fold ULN and ALP < 2-fold ULN. A listing of patients that met one or more of the Hy's Law criteria will be generated.

6.5.4 Vital Signs

Descriptive statistics for vital sign parameters (systolic and diastolic blood pressure, heart rate, temperature, and weight) and changes from baseline will be presented by visit. A listing by patient and assessment timepoint will be generated.

6.5.5 Electrocardiograms (ECG)

ECG assessments will be performed at the Screening Visit and as clinically indicated. If triplicate readings are recorded, the average of the readings for the visit will be used for the summary. Descriptive statistics for baseline ECG parameters will be presented.

The number and percentage of patients satisfying the following QT and QTcF conditions at any time post-baseline will be summarized:

- 450, > 480, or > 500 msec
- ≤ 30 msec increase from baseline, > 30 and ≤ 60 msec increase from baseline, or > 60 msec increase from baseline

6.5.6 ECOG

ECOG performance status will be summarized at each visit. Shift tables assessing the ECOG performance status at baseline versus worst performance status post-baseline will be presented.

6.6 PK ANALYSES

Plasma PK samples were collected at the scheduled time of collection (i.e. Cycle 1 Day 1 [2-hour postdose] and Cycle 2 Day 1 [predose and 2-hour postdose]). PK concentration data will be tabulated and summarized by timepoint. Descriptive statistics will include means, medians, ranges, standard deviations and coefficient of variation (CV), and geometric mean, geometric CV as appropriate.

7 INTERIM ANALYSIS

No formal interim analyses are planned for this study.

8 CHANGES IN THE PLANNED ANALYSIS

Not applicable.

9 REFERENCES

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APPENDIX A. IMPUTATION OF MISSING OR PARTIALLY MISSING DATES

In general, missing or partial dates will not be imputed. 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 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 of the month

If end date of a medication is 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 start date or end date of medication is completely missing, do not impute. If the imputed medication end date > last known alive date or end of study date, then set to the 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 AE is partially missing, the date will be imputed to determine whether the AE is treatment-emergent. When in doubt, the AE will be considered treatment-emergent by default. The following rules will be applied to impute partial dates for AEs:

If the start date of an AE 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 the 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 the 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 the end date is completely missing, do not impute.
- If the imputed AE end date > last known alive date or end of study date, then set to the 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 01Jan or the last date of a 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 a patient known to be alive +1, whichever is later.

A.4 New Anticancer Therapy

If the start day of a new anticancer treatment, radiotherapy, or surgery is incomplete or missing, impute as follows:

- If only day is missing, then the imputed day will be the first day of the month; if the imputed anticancer treatment start date is prior to the study treatment end date, change the imputed anticancer treatment start date as 'study treatment end date'.
- No imputation will be performed for all other types of missing dates.

A.5 Date of Diagnosis or Date of Progression to Any Prior Therapy

If an initial diagnosis date or disease progression date to any prior therapy is 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 of the month.
- If a diagnosis date or progression date is completely missing, do not impute.

A.6 Prior Therapies, Radiotherapies, or Surgeries

If the start date of a prior therapy, radiotherapy, or surgery date is missing, impute as follows:

- If only day is missing, then set to the first of the month.
- If both month and day are missing, then set to January 01
- If the imputed start date > first dose date then set to the first dose date -1

If the end date of a prior therapy, radiotherapy, or surgery date is missing, impute as follows:

- If only day is missing, then set to the last of the month.
- If both month and day are missing, then set to December 31
- If the imputed end date > first dose date then set to the first dose date -1

A.7 Date of Last Study Drug Administration

When the end date of a study drug administration is partially missing, the date will be imputed to calculate the extent of exposure and to define the duration of the TEAE. The following rules will be applied to impute the partial dates for the end date of a study drug administration:

- If both month and day are missing, then set to the start date of the corresponding cycle.
- If only day is missing, then the imputed day will be the first day of the month or the start date of the corresponding cycle if they have the same month and year, whichever is later.

APPENDIX B. ADVERSE EVENTS OF SPECIAL INTEREST CATEGORIES AND SEARCH CRITERIA

AESI Category	Search Criteria
Hemorrhage	Haemorrhage terms (excluding laboratory terms) (SMQ) Narrow
Major hemorrhage - Defined as serious or ≥ Grade 3 bleeding at any site, or central nervous system bleeding of any grade	Major haemorrhage: Subdural haematoma PT, Subdural haemorrhage PT All haemorrhage PTs if AE SOC is "Nervous system disorders" or Serious or ≥ Grade 3 haemorrhage PT if AE SOC is not "Nervous system disorders"
Atrial fibrillation and/or flutter	Atrial fibrillation PT, Atrial flutter PT
Hypertension	Hypertension (SMQ) Narrow
Second primary malignancies Skin cancers	Malignant tumours (SMQ) Narrow Subcategory - Skin malignant tumours (SMQ) narrow
Tumor lysis syndrome	Tumour lysis syndrome (SMQ) Narrow
Infection Opportunistic Infections	Infections: Infections and Infestations SOC Subcategory - Opportunistic infections: Opportunistic infections (SMQ) Narrow
Neutropenia	Neutropenia PT, Neutrophil count decreased PT, Febrile neutropenia PT, Agranulocytosis PT, Neutropenic infection PT, Neutropenic sepsis PT
Thrombocytopenia	Thrombocytopenia PT, Platelet count decreased PT
Anemia	Anaemia PT, Haemoglobin decreased PT