STATISTICAL ANALYSIS PLAN

Study Protocol Number:	BGB-3111_BGB-A317_Study_001
Study Protocol Title:	A Phase 1b, Open Label, Multiple Dose, Dose Escalation, and Expansion Study to Assess Safety, Tolerability, and Antitumor Activities of the Combination of BGB-3111 with BGB-A317 in Subjects with B-Cell Lymphoid Malignancies Version 5.0, 02 May 2019
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ADA	Anti-drug antibody
AE	Adverse event
ATC	Anatomical therapeutic chemical
BOR	Best overall response
BP	Blood pressure
BMI	Body mass index
CLL	Chronis lymphoid lymphoma
CR	Complete response
CRF	Case report form
CSF	Cerebrospinal fluid
CT	Computed tomography
CNSL	Central nervous system lymphoma
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose limiting toxicity
DLTS	DLT analysis set
DOR	Duration of response
EAS	Efficacy evaluable analysis set
ECG	Electrocardiograms
ENR	All subjects enrolled set
FL	Folic lymphoma
GCB	Germinal center B-cell
HCL	Hairy cell leukemia
MedDRA	Medical dictionary for regulatory activities
MR	Marginal response
MTD	Maximum tolerable dose
NE	Not evaluable
NHL	Non-Hodgkin’s lymphoma
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression free survival
PK	Pharmacokinetic
PCNSL	Primary central nervous system lymphoma
PR	Partial response
PT	Preferred term
QD	Once-daily
Q3W	One every 3 weeks
PET	Positron emission tomography
RP2D	Proposed phase 2 dose
RT	Richter’s transformation
SAP	Statistical analysis plan

SCNSL	Secondary central nervous system lymphoma
SD	Sustained disease
SMC	Safety Monitor Committee
SOC	System organ class
TEAE	Treatment-emergent adverse event
TIL	Tumor-infiltrating lymphocytes
VGPR	Very good partial response
WHO DD	World health organization drug dictionary
WM	Waldenstrom macroglobulinemia

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 results for protocol BGB-3111_BGB-A317_Study_001: A Phase 1b, Open-Label, Multiple-Dose, Dose Escalation, and Expansion Study to Assess Safety, Tolerability, and Antitumor Activities of the Combination of BGB-3111 with BGB-A317 in Subjects with B-Cell Lymphoid Malignancies. This SAP is based on the clinical study protocol Version 5.0, dated 02 May 2019.

The focus of this SAP is for the planned final analysis specified in the study protocol. This SAP documents the planned final primary statistical analyses of efficacy and safety data in the study protocol and describes the corresponding data presentations. It also documents additional efficacy and safety analyses not specified in the protocol, which will provide supplementary information to further support the safety and efficacy of the combination therapy of BGB-3111 (Zanubrutinib) and BGB-A317 (Tislelizumab).

The study also evaluates the Pharmacokinetic (PK), Pharmacodynamics, Pharmacogenomics and [redacted] The analysis details for PK, pharmacodynamics, and [redacted] are not described within this SAP.

The BeiGene Biostatistics and Statistical Programming will perform the statistical analysis detailed in this SAP; SAS (Version 9.3 or higher) will be used to generate all statistical outputs (tables, figures, listings, and datasets). The SAP will be finalized and approved prior to final database lock.

2 STUDY OVERVIEW

Study BGB-3111_BGB-317_Study 001 (hereafter referred to as Study 001) is a Phase 1b study to evaluate safety, tolerability, and preliminary efficacy of zanubrutinib in combination with tislelizumab in subjects with B-cell malignancies, including relapsed/refractory CLL/SLL, MCL, non-GCB DLBCL, GCB DLBCL, FL, MZL, HCL, transformed FL, Richter's transformation (RT), primary central nervous system lymphoma (PCNSL), and secondary central nervous system lymphoma (SCNSL) of breast or testicular origin (Note: WM subjects are excluded from enrollment as of Amendment 3). The study is divided into a dose escalation and dose expansion.

Study Treatment:

Zanubrutinib will be administered orally every day (either once daily or twice a day) with or without food. Tislelizumab will be administered intravenously (2.0 mg/kg, 5.0 mg/kg, or 200 mg flat dose, depending on assigned dose level cohort) every 21 days (Q3W). When the 2 study drugs are administered on the same day (except on the days both PK samples are collected), zanubrutinib should be taken at least 30 minutes before tislelizumab infusion.

For dose escalation, Cycle 1 will be 28 days and all subsequent cycles will be 21 days. Zanubrutinib will be administered on Cycle 1 Day 1 and then continuously every day. Tislelizumab will be administered on Cycle 1 Day 8 and then on Day 1 of all subsequent cycles. The period for DLT assessment is 21 days from Cycle 1 Day 8 to Cycle 1 Day 28.

For dose expansion, all cycles will be 21 days. On Day 1 of each cycle, zanubrutinib and tislelizumab will be administered on the same day, except for 10 subjects of the CNS lymphoma

cohort (Cohort 4A). For PCNSL and SCNSL (Cohorts 4A and 4B), 10 subjects (Cohort 4A) will initially receive single-agent tislelizumab for 4 cycles at 200 mg intravenously Q3W. On Day 1 of Cycle 5 and thereafter, these 10 subjects will receive combination zanubrutinib and tislelizumab at the RP2D defined by dose escalation.

Subjects will continue to take zanubrutinib and tislelizumab as scheduled until one of the events listed in protocol Section 4.2.4.3 occurs. There is no maximum duration of treatment as specified in the protocol. Subjects who discontinue study drug due to reasons other than disease progression will remain on study and be followed every 3 months for the survival follow-up.

Dose Escalation

The purpose of dose escalation is to determine the maximum tolerable dose (MTD) for this study. During dose escalation, three dose levels will be explored in the following order:

- Dose level 1: zanubrutinib 320 mg QD in combination with tislelizumab 2.0 mg/kg Q3W. If Dose Level 3 has cleared, subjects will be converted to dose level 3 dosing.
    - Dose level -1 (applicable only if dose level 1 exceeds MTD): zanubrutinib 160 mg QD in combination with tislelizumab 2.0 mg/kg Q3W. Further reductions of zanubrutinib or tislelizumab dose levels may be allowed until a safe dose combination is identified.
- Dose level 2: zanubrutinib 320 mg QD with tislelizumab 5.0 mg/kg Q3W. If dose level 3 has cleared, subjects will be converted to dose level 3 dosing.
- Dose level 3: zanubrutinib 160 mg BID with tislelizumab 200 mg flat dose Q3W

Dose escalation will follow the same principles as stipulated for a standard 3+3 dose escalation design, with each cohort evaluated for safety based on the number of dose-limiting toxicities (DLTs) observed (See Appendix 10.3). Evaluation of a cohort of at least 3 subjects completing the DLT assessment at any given dose level is required prior to determining the next dose level and dose regimen for the subsequent cohort. Three subjects in the cohort are sufficient if no DLTs are observed within the DLT window for all 3 subjects. More than 3 subjects are required per cohort depending on the number of observed DLTs as follows:

- < 6 subjects enrolled in the cohort:
    - 1 subject experiences a DLT during the DLT assessment period: the cohort must enroll a minimum of 6 subjects evaluable for DLT.
    - ≥ 2 subjects experience a DLT during the DLT assessment period: the MTD is considered to have been exceeded, and no additional subjects will be treated at the current or higher doses.
- ≥ 6 subjects enrolled in the cohort:
    - 1 subject experiences a DLT during the DLT assessment period: the cohort is considered tolerable and to not exceed the MTD.
    - $\geq 33\%$ of subjects (i.e., 2 out of 6) experience a DLT during the DLT assessment period: the MTD is considered to have been exceeded, and no additional subjects will be treated at the current or higher doses.

Additional subject(s) may be enrolled to each dose escalation cohort beyond the minimum necessary (3 for 0 DLT, 6 for 1 DLT).

The MTD is considered the dose level below that at which ≥ 2 (or ≥ 33%) subjects experience a DLT. If that does not occur at any dose level, the MTD is considered not to be reached. The RP2D will be selected by taking into account, the MTD, safety, tolerability, and PK profile, under the guidance of the Safety Monitoring Committee ([SMC]).

Once a dose level has been determined to have not exceeded the MTD, up to 9 additional subjects may be enrolled to that dose level cohort (e.g., a total of 15 subjects for a dose level found tolerable in a dose escalation cohort of 6 subjects) to provide additional safety information on that dose level prior to proceeding to the dose expansion part of the study. More than 9 additional subjects may be enrolled if requested by the SMC for additional safety information.

Dose Expansion

In the dose expansion, there will be 4 dose expansion cohorts at the RP2D for the combination of tislelizumab and zanubrutinib:

- Cohort 1 (n = 10): GCB DLBCL
- Cohort 2 (n = 10): Non-GCB DLBCL
- Cohort 3 (n = 20): Transformed lymphoid malignancy
- Cohort 4: PCNSL or SCNSL of breast or testicular origin
    - Cohort 4A (n = 10): begin with 4 cycles of single-agent tislelizumab at 200 mg Q3W, combination of zanubrutinib and tislelizumab starting Cycle 5
    - Cohort 4B (n = 10): combination of zanubrutinib and tislelizumab starting Cycle 1

The dose and schedule of combination zanubrutinib and tislelizumab will be the RP2D as determined by the SMC for the non-CNS disease types (Cohorts 1 to 3). The dose and schedule of single-agent tislelizumab will be 200 mg IV Q3W for Cohort 4 followed by the RP2D for the combination. Approximately 10 to 20 subjects each per classification of non-Hodgkin lymphoma will be enrolled in dose expansion. Cohorts 1, 2, 3, and 4A will open simultaneously once the RP2D has been determined. For Amendment 5.0, Cohort 4A is being discontinued. There were no safety or tolerability signals that led to the discontinuation of Cohort 4A. As of March 2019, 3 subjects with CNSL have been enrolled in Cohort 4A; however, no subjects remain on treatment in this cohort, which is closed to treatment and further enrollment. Cohort 4B was to be immediately activated with Amendment 5.0.

3 STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVES

- To determine the MTD and/or RP2D of tislelizumab when given in combination with zanubrutinib.
- To assess the safety and tolerability of zanubrutinib in combination with tislelizumab

(Cohorts 1 to 3 and 4B) or single-agent tislelizumab followed by the combination of zanubrutinib and tislelizumab (Cohort 4A) in previously treated subjects with B-cell malignancies.

3.2 SECONDARY OBJECTIVES

- To assess the preliminary antitumor activity of zanubrutinib in combination with tislelizumab (Cohorts 1 to 3 and 4B) or a single-agent tislelizumab followed by the combination of zanubrutinib and tislelizumab (Cohort 4A) in previously treated subjects with B-cell malignancies.
- To characterize the PK of zanubrutinib and tislelizumab when administered in combination.
- To assess host immunogenicity to tislelizumab when administered in combination with zanubrutinib.

3.3 EXPLORATORY OBJECTIVES

- [redacted]

4 STUDY ENDPOINTS

4.1 PRIMARY ENDPOINTS

- Dose escalation: The MTD and RP2D of tislelizumab in combination with zanubrutinib, as determined based on the incidence of protocol-defined dose-limiting toxicities, safety, tolerability, and PK profile.
- Dose expansion: The safety and tolerability of combination zanubrutinib and tislelizumab (Cohorts 1 to 3 and 4B) or single-agent tislelizumab followed by combination zanubrutinib and tislelizumab (Cohort 4A) in previously treated subjects with B-cell malignancies, as assessed by the occurrence and severity of AEs (Common Terminology Criteria for Adverse Events [CTCAE], version 4.03).

4.2 SECONDARY ENDPOINTS

- The antitumor activity of the combination of zanubrutinib and tislelizumab (Cohorts 1 to

3 and 4B), or single-agent tislelizumab, followed by combination zanubrutinib and tislelizumab (Cohort 4A) in previously treated subjects with specified B-cell malignancies, as determined by

- overall response rate (ORR, defined as the proportion of subjects who had CR or PR by standard disease-specific response criteria),
- duration of response ([DOR]; defined as the time from the date that a confirmed objective response is first documented to the date of PD or death due to any cause for those subjects with a confirmed PR or CR), and
- progression-free survival ([PFS]; defined as the time from the first dose of study medication to objective disease progression or death).
- drug antibody to tislelizumab when given in combination with zanubrutinib.

4.3 EXPLORATORY ENDPOINTS

- [redacted]

5 SAMPLE SIZE CONSIDERATIONS

The number of dose levels in the dose escalation and the emerging zanubrutinib and/or tislelizumab toxicities will determine the sample size. It is anticipated that approximately 15 subjects per dose level will be required to complete the dose escalation of the study, and approximately 60 subjects (anticipated that approximately 10 subjects per cohort for Cohorts 1 and 2 and 20 subjects per cohort for Cohorts 3 and 4) will be required to complete the dose expansion of the study. Subjects dropping out before completion will be replaced by enrolling a new subject.

6 STATISTICAL METHODS

6.1 ANALYSIS POPULATIONS

The following analysis sets will be defined, i.e., Safety analysis sets in dose escalation and in dose expansion, and DLT analysis set.

Safety analysis set: Includes all subjects who receive at least 1 dose of zanubrutinib and/or tislelizumab. The safety analysis set will be further separated in dose escalation and in dose expansion. The safety analysis set combining dose escalation and dose expansion will be used primarily for all summaries, both safety and efficacy analyses, except selected DLTs and AE summaries as described in Section 6.2.

DLT analysis set: Includes all subjects evaluated by the Study Monitor Committee (SMC) for DLTs. The database was not built to capture whether a given patient experienced a DLT. Both DLT analysis set and AEs considered DLTs were identified by SMC review and documented in SMC meeting minutes.

6.2 Data Analysis General Considerations

At the time of finalization of the SAP, enrollment to the study has closed. Table 6-1 below summarizes the number of subjects enrolled according to disease type and study treatment. The small number of some disease types were considered in the analyses plan.

Table 6-1 Number of subjects with different B-cell malignancy enrolled into the study by actual dose levels

	Zanu 320 mg QD Tisle 2.0 mg/kg	Zanu 320 mg QD Tisle 5.0 mg/kg	Zanu 160mg BID Tisle 200 mg	Total
Dose escalation	15	10	7	32
WM	0	2[1]		2
CLL	3	2		5
NHL	12	6	7	25
MCL	1	1		2
MZL	1			1
FL	3	2	1	6
GCB DLBCL	2		2	4
Non-GCB DLBCL	1	2	2	5
Richter's Transformation (RT)	1		1	2
Transformed FL	3	1	1	5
Dose expansion (NHL)			43	
GCB DLBCL (Cohort 1)			8	
Non-GCB DLBCL (Cohort 2)			10	
Transformed malignancy (Cohort 3)			20 (4 RT+16 Transformed FL)	
PCNSL + SCNSL (Cohort 4A and 4B)			5 (3 for primary+2 for secondary) [2]	

Dose escalation + expansion	15	10	50	75
WM	0	2[1]		2
CLL	3	2		5
NHL	12	6	50	68
MCL	1	1		2
MZL	1			1
FL	3	2	1	6
GCB DLBCL	2		10	12
Non-GCB DLBCL	1	2	12	15
Richter's transformation	1		5	6
Transformed FL	3	1	17	21
PCNSL + SCNSL			5 (3 for primary+2 for secondary) [2]	5

Abbreviation: Zanu: Zanubritinib (BGB-3111); Tisle: Tislelizumab (BGB-A317)
Note:
[1] One Subject with WM disease planned to receive Zanu 320 mg QD + Tisle 2.0 mg/kg but received Zanu 320 mg QD + Tisle 5.0 mg/kg.
[2] Two subjects from dose expansion cohort 4A did not receive Zanu before treatment discontinuation.

Dose Escalation

Subjects that are part of the safety analysis set that were enrolled into the dose escalation portion of the study (or DLT analysis set for DLT summary) will be summarized by the following dose levels (as first received dose level) and overall:

- Dose level 1: zanubrutinib 320 mg QD plus tislelizumab 2.0 mg/kg Q3W
- Dose level 2: zanubrutinib 320 mg QD plus tislelizumab 5.0 mg/kg Q3W
- Dose level 3: zanubrutinib 160 mg BID plus tislelizumab 200 mg flat dose Q3W

During the study conduct, the dose level 3 was cleared and identified as the RP2D. Subjects from dose escalation, originally assigned to dose levels 1 and 2, were thereafter switched to the dose level 3. The analyses for dose escalation phase will be limited to the period before subject receive their first level 3 dose for subjects originally assigned to dose levels 1 and 2.

Analyses for these dose escalation cohort will limit to disposition, baseline and selected safety analyses including TEAE summary table, TEAE summary by SOC and PT, and DLT summary per SMC reviews and meeting minutes.

Dose Escalation + Dose Expansion

Driven by the small number of subjects with different B-cell lymphoid malignancies under different doses, the main safety analyses will primarily be performed based on safety analysis set

combining the dose escalation cohort and the dose expansion cohort, by the following disease types and overall:

- Other B-cell lymphoid malignancies, including WM, CLL, MCL, MZL, and FL. If data indicates a particular malignancy is of interest, additional disease-specific analysis may be considered post hoc.
- DLBCL
  - GCB DLBCL
  - Non-GCB DLBCL
  - Subtotal
- RT
- Transformed FL
- CNS lymphoma, defined as subjects with either PCNSL or SCNSL. If data indicates a particular malignancy is of interest, additional disease-specific analysis may be considered post hoc.

6.2.1 Definitions and Computations

Study day: Study day will be calculated in reference to the date of the first dose of 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 10.4

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

Unscheduled Visits: Unscheduled visit measurements will be included in listings and for derivation of 1) baseline values, and 2) the analysis of max/min values and max/min changes from baseline values and related shift tables. Unscheduled measurements will not be included in by-visit table summaries and graphs.

Repeated Measurements: For repeated measurements, i.e., measurements with exact same collection date and time (if time is available) and source (central vs. local lab), the average of the repeated measurements will be used to reflect the value at the corresponding measurement date and time. Actual values will be presented in the data listings.

6.2.2 Conventions

Unless otherwise specified, the following conventions will be applied to all analyses:

- 1 year = 365.25 days. Number of years is calculated as (days/365.25) rounded up to 1 significant digit.
- 1 month = 30.4375 days. Number of months is calculated as (days/30.4375) rounded up to 1 significant digit.

- Age will be calculated as the integer part of (date of informed consent – date of birth + 1)/365.25
- P-values will be rounded to 4 decimal places. P-values that round to 0.0000 will be presented as '< 0.0001' and p-values that round to 1.000 will be presented as '> 0.9999'.
- Time-to-event or duration of event endpoints will be based on response assessment dates per the investigators.
- Missing efficacy or safety data will not be imputed unless otherwise specified.
- For laboratory results collected as < or >, a numeric value, 0.0000000001 will be subtracted or added, respectively, to the value.
- For by-visit observed data analyses, percentages will be calculated based on the number of patients with non-missing data as the denominator, unless otherwise specified.
- For continuous endpoints, summary statistics will include n, mean, standard deviation, median, Q1, Q3 and range (minimum and maximum).

6.2.3 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 and prior/concomitant medications/procedures. Specific rules for handling of missing or partially missing dates for adverse events and prior/concomitant medications/procedures are provided in Appendices 10.4.

By-visit assessments 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.

6.2.4 Adjustment for Covariates

With possible exception of exploratory analyses, no adjustments for covariates are planned for this study. [redacted]

6.2.5 Multiplicity Adjustment

Given the phase 1b, dose escalation and expansion study design, and the primary safety objective of the study, there is no multiplicity adjustment.

6.2.6 Data Integrity

Before pre-specified interim or final 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 subjects' relevant outcomes from the clinical database. All data should be complete and reviewed up to a pre-specified cutoff date. Consistency checks and appropriate source data verification should be complete.

6.3 SUBJECT CHARACTERISTICS

6.3.1 Subject Disposition

The number (percentage) of subjects treated, discontinued from study treatment and discontinued from the study will be summarized. The primary reason for end of treatment for zanubrutinib and tislelizumab separately, and the primary reason for end of study will be summarized by categories.

The study follow-up time, defined as the time from first dose of study treatment to study discontinuation will also be summarized. Survival status (alive, death, or lost to follow-up) at the study discontinuation will be summarized.

6.3.2 Protocol Deviations

Major protocol deviation criteria will be established and subjects with major protocol deviations will be identified and documented before the database lock. Major protocol deviations will be summarized based on safety analysis set. They will also be listed by each category.

6.3.3 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized using descriptive statistics in the safety population. Continuous variables include height, weight, BMI; categorical variables include the following

- Sex,
- Age (years) and age group (< 65 y ears vs. ≥ 65 years),
- Race,
- Ethnicity,
- Geographic region and country (China vs. Australia),
- Eastern Cooperative Oncology Group (ECOG) performance status
- Height (cm), weight (kg) and Body mass index (BMI in kg/m2)

6.3.4 Disease History

The number (percentage) of subjects reporting a history of disease and characteristic, as recorded on the CRF, will be summarized. Disease characteristics include

- Time from first diagnosis of B-cell lymphoid malignancies (months),
- Disease type (CLL, NHL, WM)
    - For CLL, type, stage at initial diagnosis and at study entry; genotype status for del(17p), del(11q), del(13q), trisomy 12, IgVH mutation, and p53 mutation
    - For NHL, type, stage at initial diagnosis and at study entry
    - For WM, stage at initial diagnosis and at study entry

A listing of disease characteristics/history will be provided.

6.3.5 Medical History

Medical History will be coded using MedDRA (Version 22.0 or higher). The number (percentage) of subjects reporting a history of any medical condition, as recorded on the CRF, will be summarized by system organ class and preferred term based on safety analysis set. A listing of medical history will be provided.

6.3.6 Prior Anti-Cancer Drug Therapies and Surgeries

The number (percentage) of subjects with any prior systematic therapy, as recorded on the CRF, will be summarized. Number of prior regimens, both as continuous variable and in categories (1, 2, 3, 4, 5, and >=6) will be summarized. Of the last therapy, their duration, best response, time from last therapy to first dose, and time from disease progression on most recent systemic therapy to first dose will be summarized as well.

The number (percentage) of subjects with prior radiation therapy, the time from the last radiation therapy to first dose and site of the radiation therapy will be summarized.

6.3.7 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO DD) drug codes (Version B3 Sep 2018 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. Concomitant medications will be 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 after the subject's last dose or initiation of a new anti-cancer therapy. For the purpose of determining if a medication should be noted as a concomitant medication, the imputation rules stated in Appendix 10.4.1 will be used.

The number (percentage) of subjects reporting prior and concomitant medications will be summarized by ATC medication class and WHO DD preferred term. A listing of prior and concomitant medications will be provided.

6.4 EFFICACY ANALYSIS

6.4.1 Primary Endpoint

The study's primary objectives and endpoints are all related to safety. Please refer to Section 6.5 for the primary safety analyses. The section below describes the analyses for the secondary endpoints on efficacy, including ORR, DOR, and PFS, and additional endpoints including OS and others.

6.4.2 Secondary Endpoints

Note: Response related analyses will be based on the disease response page, with PD based on disease progression page. Given the design of disease progression page, if a subject reported 'Yes' to disease progression but only '*Death*' is checked as the *'primary method of detection of progression disease'*, the subject will not be considered as having PD. Instead the information will be summarized in the summary of death.

All efficacy analyses will be based on Safety Analysis Set, unless specified otherwise.

6.4.2.1 Best Overall Response (BOR) and Overall Response Rate (ORR)

The response and progression status were determined by the investigator using the appropriate disease-specific criteria defined in the protocol. Please refer to Appendix 10.1 for the schedule of related assessments.

A subject's best overall response is the best disease response recorded throughout the study. The assessment after documented disease progression will be excluded from the BOR derivation. Disease responses recorded after initiation of new anti-cancer treatment will not be considered for best overall response. Subjects without postbaseline disease assessments will be grouped as NE and considered as non-responders. The best overall response (number [%]) will be summarized.

Note that for NHL, the response may be evaluated by either PET or CT, and the response results were collected separately. In the response analyses, these responses will be combined as in the first column in Table 6-2. The BOR will be derived combining results from PET and CT.

Table 6-2 NHL responses either by PET or by CT (per Investigator)

Response	**NHL per PET**	**NHL response per CT**
CR	CMR	CR
PR	PMR	PR
SD	NMR	SD
PD	PMD	PD
NE	NE	NE

ORR is the proportion of subjects with best overall responses in the categories constituting response for each disease type. For each specific disease, Table 6-3 shows the response categories included in ORR by diseases. ORR will be summarized, along with Clopper Pearson 2-sided 95% confidence interval.

Table 6-3 ORR response categories by diseases

	Responses included in ORR
WM	CR, VGPR, PR, MR
CLL*	CR, PR
NHL (except below)	CR, PR
PCNSL + SCNSL	CR, CRu, PR

*For CLL subjects, potential nPR or PR-L were not collected in the database

A swimlane plot will be provided to summarize the subjects' response over time.

6.4.2.2 Progression Free Survival (PFS)

Progression-free survival (PFS) is defined as the time (in months) from the date of first study treatment to the first documented disease progression or death (due to any reason, unless happened after more than 6 months since last disease assessment, i.e., see Condition 5 in Table 6-4), whichever occurs first.

PFS will be right-censored for patients who met one of the following conditions: 1) no postbaseline disease assessments; 2) starting a new anti-cancer 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 6-4.

Table 6-4: Date of Progression or Censoring for Progression-Free Survival

Situation	Date of Progression Event	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 disease assessment	Date of death	Event
3. No postbaseline disease assessments	Date of first dose	Censored
4. New anti-cancer treatment started before PD or death	Date of last disease assessment before start of new anti-cancer treatment	Censored
5. Death or PD more than 6 months[1] after last disease assessment visit	Date of last disease assessment before death or PD	Censored
6. Alive and without PD	Date of last disease assessment	Censored
[1] Or 12 months if a subject is on the assessment schedule of every 24 weeks (not applicable for the study in discussion as assessments are every 12 weeks).		

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

In addition to the endpoints defined per protocol in Section 5.2, the following efficacy endpoints will also be analyzed.

6.4.2.3 Duration of response (DOR)

Duration of response for responders (DOR) is defined as the time interval (in months) from the date of the earliest qualifying response to the date of PD or death for any cause (whichever occurs earlier). Only subjects who have achieved overall responses will be included in the analysis of

DOR. DOR will be determined using the same censoring rules as those specified for PFS in Section 6.4.2.2. DOR will be analyzed using the same methods as in the analysis of PFS.

A similar analysis will be conducted for duration of response for complete responders.

6.4.3 Additional Efficacy Endpoints

6.4.3.1 Time to Response

Time to response (TTR) for responders is defined as time (in months) from the start of the study treatment to the date of the earliest qualifying response. Time to overall responses, and time to complete responses will be summarized by descriptive statistics.

6.4.3.2 Overall Survival (OS)

OS is defined as the time from the date of first study dose to death. Subjects who remained alive before discontinuation of the study (discontinued study due to reasons other than "Death") will be censored at the last date the subject was known to be alive. Kaplan-Meier curve will be used to estimate OS at different time points.

6.4.3.3 MRD for CLL

MRD data will only be listed for subjects with CLL because there are only 2 CLL subjects enrolled.

6.5 SAFETY ANALYSES

Two sets of analyses will be performed. One set will be for dose escalation by doses based on safety analysis set in dose escalation cohort for selection analyses as specified in Section 6.1; the main analyses will be performed combining dose escalation cohort and expansion cohort, by disease subtypes, based on safety analysis set.

The incidence of treatment-emergent adverse events (TEAEs), as defined in Section 6.5.2, will be summarized. Laboratory test results, vital signs and their changes from baseline will be summarized using descriptive statistics (e.g., n, mean, standard deviation, median, Q1, Q3, minimum, maximum for continuous variables; n [%] for categorical variables. These results will be listed. Abnormal values will be flagged.

6.5.1 Extent of Exposure

The treatment exposure will be summarized separately for zanubrutinib and tislelizumab separately. For both drugs, their cumulative dose administered, planned dose intensity, actual dose intensity, and relative dose intensity will be summarized respectively.

For zanubrutinib,

- The duration of treatment (days) is calculated as (date of the last dose – date of first dose + 1). In addition to the continuous summary, it will also be summarized by categories (< 3months, 3-<6 months, 6-<9 months, 9-<12 months, 12-<24 months and >24 months).
- The planned dose intensity is defined as the planned starting zanubrutinib dose per day (320

mg/day).

- The actual dose intensity is defined as the cumulative dose (mg) taken based on the total daily dose divided by the duration of zanubrutinib treatment (days).

For tislelizumab,

- The duration of treatment (weeks) is calculated as (date of last dose + 21 days − date of first dose)/7
- The planned dose intensity (mg/wk) is defined as the planned dose per week:
    - For subjects in dose escalation dose levels 1 and 2 with some subjects later switched to the 200 mg /kg Q3W dosing schedule, the planned dose intensity will be the ratio of cumulative planned dose/(number of cycles x 3). The cumulative planned dose will be calculated as the sum of last weight prior to infusion x (2.0 or 5.0) mg/kg for all relevant cycles plus 200 mg times number of cycles after dosing switch) divided 3 (Q3W schedule);
    - For subjects in dose escalation dose level 3 and in dose expansion, the planned dose intensity is 200 mg Q3W (66.7 mg/wk).
- The actual dose intensity is defined as the cumulative dose (mg) divided by the duration of treatment (mg/wk).

For both zanubrutinib and tislelizumab

- The relative dose intensity (RDI) is defined as the ratio of the actual dose intensity to the planned dose intensity in percentage.

In addition, for zanubrutinib, the number (percentage) of subjects with dose change and the number of dose change per subject; the number (percentage) of subjects with dose interruption, the number of dose interruption per subject, and duration of dose interruption; the number of subjects with dose missed and the number of dose missed per subject will be summarized.

For tislelizumab, a listing of dose interruption will be provided. Dose delays were not captured in the data and can only be inferred based on relative dose intensity described above. The cycle in which the first dose interruption/delay occurred will be summarized.

6.5.2 Adverse Events

AEs will be graded by the investigators using CTCAE v4.03. The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 22.0 or higher) lower level term closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A treatment-emergent adverse event (TEAE) is defined as an AE that had an onset date during the treatment-emergent period, defined as from the first dose date of Zanubrutinib or Tislelizumab (whichever is earlier) through 30 days after the last dose (permanent discontinuation of study drug) of Zanubrutinib or 90 days after the last dose of Tislelizumab, whichever is later, or prior to initiation of new anti-cancer therapy. Treatment-related SAEs and any worsening of a TEAE by PT post treatment-emergent period will be also be counted as TEAEs. Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

An overview table, including the number (percentage) of subjects with the following, will be provided.

- TEAEs,
- TEAEs with grade 3 or above,
- Treatment-emergent serious adverse events (SAEs),
- TEAEs that led to treatment discontinuation,
- TEAEs that lead to treatment modification, by dose reduction vs. dose interruption.
- TEAEs that led to death

And

- Treatment-related TEAEs,
- Treatment-related TEAEs with grade 3 or above,
- Treatment-related Treatment-emergent serious adverse events (SAEs),
- Treatment-related TEAEs that led to treatment discontinuation,
- Treatment-related TEAEs that lead to treatment modification, by dose reduction vs. dose interruption.
- Treatment-related TEAEs that led to death

Treatment-related AEs or SAEs include those events considered by the investigator to be related to either Zanubrutinib or Tislelizumab or with missing assessment of the causal relationship.

TEAEs that lead to treatment discontinuation, dose reduction or dose interruption include those events that lead to discontinuation, dose reduction or dose interruption of either Zanubrutinib or Tislelizumab. The worst action (in the order of treatment reduction < interruption < discontinuation) will be selected as the action in the summary.

The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once by the highest severity grade according to CTCAE v.4.03 within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT.

The number (percentage) of subjects with the following will be summarized by SOC and PT.

- TEAEs
- TEAEs with grade 3 or above,

- SAEs
- TEAEs that led to treatment discontinuation,
- TEAEs that lead to dose modifications, including dose reduction or dose interruption
- TEAEs that led to death
- Treatment-related TEAEs,
- Treatment-related SAEs,

TEAEs with grade 3 or above will also be summarized by PT in descending order.

Additional AEs of Special Interest (AESIs) for Zanubrutinib and Immuno-related AEs (irAEs) will be identified per the Search strategy for the corresponding compound. Both AESIs and irAE will be summarized by SOCs and PTs.

Subject data listings of all AEs, SAEs, treatment-related AEs, grade 3 or above AEs, AEs that led to death and AEs that led to treatment discontinuation of either Zanubrutinib or Tislelizumab will be provided.

6.5.2.1 Death

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

6.5.2.2 Dose Limiting Toxicities

The database was not built to identify the subject with DLT. A subset of subjects enrolled into the dose escalation were reviewed by SMC. The DLTs were identified based on SMC review and meeting minutes and will be described in the CSR directly without further analyses.

6.5.3 Laboratory Values

Laboratory safety tests were evaluated per protocol (Appendix 10.5). Descriptive summary statistics for laboratory parameters (clinical chemistry, hematology, and coagulation results) and their changes from baseline will be summarized by visit.

Laboratory parameters (ALP, ALT, AST, total bilirubin, albumin, hemoglobin, platelet counts, WBC count, neutrophil and lymphocyte) that are graded in NCI CTCAE (v.4.03) will be summarized by shifts from baseline CTCAE grades to maximum post-baseline grades. In the summary of laboratory parameters by CTCAE grade, parameters with CTCAE grading in both high and low directions will be summarized separately.

Subject data listings of selected hematology and serum chemistry parameters, urinalysis and coagulation will be provided.

6.5.4 Vital Signs

Descriptive statistics for vital sign parameters (systolic and diastolic blood pressure [BP], pulse rate, temperature, and weight) and changes from baseline will be presented by visit. Vital signs will be listed by subjects and visits.

6.5.5 Physical Examination

Subjects with abnormal physical exams will be listed.

6.5.6 Echocardiogram

The overall evaluation and LVEF (%) at screening will be listed without summary.

6.5.7 Electrocardiograms (ECG)

ECG will be performed at the baseline and multiple time points after the start of treatment. ECG findings at baseline, post-baseline visits and change from baseline will be summarized.

6.5.8 ECOG

A shift table from baseline to worst post-baseline in ECOG performance score will be summarized. ECOG scores will be summarized by visit.

6.5.9 Ophthalmologic exam

Ophthalmologic exams were added in the protocol amendment and only limited number of subjects have both baseline and post baseline assessments. No further tabulation will be generated for Ophthalmologic results.

Subjects' ophthalmologic exam will be listed.

7 INTERIM ANALYSIS

There were no formal interim analyses conducted for this study. As specified in the Protocol Section 4.1.2, the continuous safety evaluation was performed by the sponsor, the coordinating investigator, and investigators, and the Safety Monitoring Committee (SMC). Please refer to SMC charter and meeting minutes for related information as needed.

Additional analyses were conducted to support multiple publication purposes.

8 SUMMARY OF MODIFICATIONS

8.1 MODIFICATIONS FROM THE APPROVED CLINICAL STUDY PROTOCOL

Protocol Section	Protocol Language	SAP Section and Language	Rationale
NA	**NA**	**Section 6.1** The safety analysis set will be used primarily for all summaries, both safety and efficacy analyses, except selected DLTs and AE summaries as described in Section 6.2. **Section 6.2** Driven by the small number of subjects with different B-cell lymphoid malignancies under different doses, the primary safety analyses will primarily be performed based on safety analysis set.	Per protocol, the 2nd bullet of the primary objective and the secondary endpoints implies the analyses will be based on subjects from dose expansion only. However, driven by the fact that there was no observed difference in subjects' safety/efficacy profile by doses during dose escalation, and to increase the number of subjects for different diseases to make the analyses more interpretable, the analyses will be based on safety analysis set combining subjects from dose escalation and expansion.
10.2.1 Analysis Set	**All subjects enrolled set (ENR)**: Includes all subjects who provide informed consent for this study.	Removed	Subjects sign informed consent at screening. Original language includes screen failure subjects. Given the open label study nature, the enrolled subjects are all dosed. The Safety analysis set defined in Section 6.1 will meet the analyses need.
10.2.1 Analysis Set	**DLT analysis set (DLTS):** Includes all subjects who	**DLT analysis set (DLTS):** Includes all subjects evaluated by the Study	DLT review is performed and identified by SMC. The analyses of DLTS and

	experienced a DLT during DLT observation period plus subjects who received at least 80% of the planned doses of treatment during the DLT observation period (Cycle 1) and had sufficient safety evaluation	Monitor Committee (SMC) for DLTs. The database was not built to capture whether a given patient experienced a DLT. Both DLT analysis set and AEs considered DLTs were identified by SMC review and documented in SMC meeting minutes.	DTLs will be based on SMC meeting minutes

8.2 MODIFICATIONS FROM THE APPROVED STATISTICAL ANALYSIS PLAN

This is the first version of the final primary Statistical Analysis Plan (SAP) for the study.

9 REFERENCES

Crowley, R. B. (1982). A Confidence Interval for the Median Survival Time. *Biometrics*, 29-41.

Greenwood, M. (1926). The natural duration of cancer. *Reports on Public Health and Medical Subjects*, 1-26.

Schemper, M., & Smith, T. L. (1926). A note on quantifying follow-up in studies of failure time. *Contemporary Clinical Trials*, 343-346.

10 APPENDIX

10.1 SCHEDULE OF ASSESSMENTS

The Schedules of Assessments are presented in Table 10-1 and Table 10-2. Sections in the footnotes are all referring to protocol sections.

Table 10-1 Schedule of Assessments (Dose Escalation for Dose Levels 1, 2, and 3)

	Screening[1]	Treatment Period[2]						Safety Follow-up[3]	Efficacy Follow-up[3]	Survival Follow-up[4]
		Cycle 1 (DLT Period: 21 days from D8 to D28)					Cycle 2 and Additional Cycles (21 days)			
Days Window	**-28 to -1**	**D1**	**D2**	**D8**	**D15 ± 1**	**D22 ± 1**	**D1 ± 3**	**30 ± 3 Days After Last Dose (Telephone Contacts 60 & 90 ± 14 Days After Last Dose)**	**Every 3 Months ±7 Days**	**Every 3 Months ±7 Days**
Informed consent	X									
Inclusion/exclusion criteria	X									
Demographic/medical history	X									
Vital signs/weight[5]	X	X	X	X	X	X	X	X	X	
B symptoms[6]	X	X	X	X	X	X	X	X	X	
Complete physical examination[7]	X									
Targeted physical examination[7]		X		X	X	X	X	X	X	
ECOG performance status	X	X		X			X	X		
Echocardiogram or MUGA	X									
12-lead ECG[8]	X	X	X	X	X	X	X	X		
Review AEs[9]		X	X	X	X	X	X	X		
Review concomitant medications	X	X		X	X	X	X	X		

	Screening[1]	Treatment Period[2]						Safety Follow-up[3]	Efficacy Follow-up[3]	Survival Follow-up[4]
		Cycle 1 (DLT Period: 21 days from D8 to D28)					Cycle 2 and Additional Cycles (21 days)			
Days Window	**-28 to -1**	**D1**	**D2**	**D8**	**D15 ± 1**	**D22 ± 1**	**D1 ± 3**	**30 ± 3 Days After Last Dose (Telephone Contacts 60 & 90 ± 14 Days After Last Dose)**	**Every 3 Months ±7 Days**	**Every 3 Months ±7 Days**
Hematology[10]	X	X	X	X	X	X	X	X	X	
Clinical chemistry[11]	X	X	X	X	X	X	X	X	X	
Coagulation parameters	X	X					X	X		
Urinalysis[12]	X	X		X	X	X	X	X		
Pregnancy test[13]	X	X					X	X		
Thyroid function[14]	X						X	X		
IgA, IgG, and IgM level [15]	X						X	X	X	
Viral serologies[16]	X									
tislelizumab administration (30 to 120 minutes infusion)				X			X			
Zanubrutinib administration in clinic[17]		Orally every day								
Tumor assessment by CT scan[18]	X	Every 4 cycles						X	X[19]	
Bone marrow evaluation[20]	X	• End of Cycle 4 • To confirm CR (at any time, Cycle 4 or later)								
Overall disease response [21]		Every 4 cycles							X[22]	
CLL prognostic factors[23]	X									
Survival status										X
CENTRAL LABORATORY STUDIES										
Anti-tislelizumab				X			X	X		

	Screening[1]	Treatment Period[2]						Safety Follow-up[3]	Efficacy Follow-up[3]	Survival Follow-up[4]
		Cycle 1 (DLT Period: 21 days from D8 to D28)					Cycle 2 and Additional Cycles (21 days)			
Days Window	**-28 to -1**	**D1**	**D2**	**D8**	**D15 ± 1**	**D22 ± 1**	**D1 ± 3**	**30 ± 3 Days After Last Dose (Telephone Contacts 60 & 90 ± 14 Days After Last Dose)**	**Every 3 Months ±7 Days**	**Every 3 Months ±7 Days**
antibodies[24]										
Archival tumor tissues[25]	X									
Fresh tumor tissues[25]	X			X				X		
PK blood sampling[26]		X	X				X			
Pulmonary function tests[27]	X									
Optical coherence tomography (or equivalent diagnostic test) and visual acuity tests[28]	X						X[29]	X[29]		

ADA = anti-drug antibody; AE = adverse event; ALT = alanine aminotransaminase; AST = aspartate aminotransaminase; CLL = chronic lymphocytic leukemia; CR = complete response; CT = computed tomography; D = day; DLBCL = diffuse large B-cell lymphoma; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EPG = electrophoresis; FISH = fluorescence in situ hybridization; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IgVH – immunoglobin variable region heavy chain; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; MUGA = multigated acquisition scan; PCR = polymerase chain reaction; PD-1 = programmed cell death-1; PD-L1 = programmed death ligand-1; PD-L2 = programmed death ligand-2; PET = positron emission tomography; PK = pharmacokinetic; QTc = corrected QT wave; TSH = thyroid stimulating hormone; WBC = white blood cell.

Assessments scheduled on study drug administration days should be performed predose, unless otherwise specified.

[1] Performed within 28 days prior to Day 1. Assessments that are performed as standard of care assessments may be used for screening.

[2] The maximum duration of treatment will be until disease progression.

[3] Safety follow-up performed within 30 days after the last dose of zanubrutinib (± 3 days). If the patient continues on single-agent tislelizumab, a second safety follow-up should be performed 30 days after last dose of tislelizumab. Telephone contacts with patients should be conducted to assess AEs and concomitant medications (if appropriate, ie, associated with an AE or is a new anticancer therapy) at 60, and 90 days (±14 days) after the last dose of tislelizumab (see Section 7.4). Efficacy follow-up will apply only to subjects who discontinue study drug due to reasons other than disease progression. They will remain on study and should follow the guidance provided in Section 7.5.

[4] Once subjects progress or start the use of alternative anti-cancer therapy, subjects only need to establish survival status and are not required to come in for a visit. (see Section 7.6.)

[5] Vital sign time points for PK sampling will be obtained per Table 4-3.

[6] Unexplained weight loss > 10% over previous 6 months, fever (>38°C), and/or drenching night sweats.

[7] Complete physical exam includes all systems described in the body of the protocol. Targeted physical exams should be limited to systems of clinical relevance (i.e., cardiovascular, respiratory, lymph nodes, liver, and spleen) and those systems associated with clinical signs/symptoms.

[8] Perform a 12-lead ECG in triplicate at screening and at the treatment completion/early termination visit. ECG time points for PK sampling will be obtained as per Table 4-3. Additional ECGs may be required if there is a prolongation of QT or QTc, see Section 7.2.3.

[9] AEs will be recorded from the time of the first dose and all SAEs will be collected after informed consent has been signed. Telephone contacts with patients should be conducted to assess AEs and concomitant medications (if appropriate, ie, associated with an AE or is a new anticancer therapy) at 60, and 90 days (±14 days) after the last dose of tislelizumab. All AEs and SAEs, regardless of relationship to study drug, will be recorded until up to 90 days after the last dose of study drug. Beyond the safety follow up period, all drug-related SAEs will be recorded by investigator until patient death, or lost to follow up, whichever occurs first.

[10] Hematology, including hemoglobin, reticulocyte count, WBC count, absolute differential count (neutrophils, eosinophils, lymphocytes) and platelet count. In the event of neutropenia (absolute neutrophil count $< 1.0 \times 10^9$/L) or thrombocytopenia (platelets count $< 50 \times 10^9$/L), assessments will be performed as frequent as the physician feels needed until toxicity resolves to ≤ Grade 2. Results of blood tests taken within 24 hours may be used to allow the investigator to make the decision to proceed with dosing; in these cases, a separate pre-treatment sample must still be taken.

[11] Clinical chemistry includes sodium, potassium, chloride, bicarbonate (total CO_2), glucose, urea, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, ALT, AST, LDH, alkaline phosphatase and uric acid. In the event of ≥ Grade 3 clinical chemistry toxicity, these assessments will be conducted as frequent as the physician feels needed until toxicity resolves to ≤ Grade 2. Results of blood tests taken within 24 hours may be used to allow the investigator to make the decision to proceed with dosing; in these cases, a separate pre-treatment sample must still be taken.

[12] Collect urine dipstick, as well as urine microscopy, if dipstick is abnormal. If urine protein is ≥2+ by dipstick, a 24-hour urine test for total protein and a random urine test for total protein and creatinine will be obtained and evaluated on the first occasion; subsequent need for 24-hour collection will be determined by the investigator. Refer to Section 7.2.1.

[13] All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening. Laboratory-based highly sensitive pregnancy tests (urine or serum) will be performed at specified subsequent visits and continued (local laboratory is acceptable) every 4 weeks for at least 90 days after the last dose of study drug. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[14] T3, T4, TSH; at screening, then every other cycle starting from Cycle 2, and at the mandatory safety follow-up visit. Additional T3, T4 and TSH may be performed at the discretion of the investigator.

[15] If a paraprotein is present, testing will be repeated on all subsequent immunoglobulin assessments. IgA, IgG and IgM tests should be performed for all subjects at screening and only for those with significant abnormal findings at subsquent visits. EPG testing was removed with Amendment #4.

[16] Viral serologies include hepatitis B (HBsAg and total HB core antibody [anti-HBc] as well as HBV DNA by PCR if the subject is HBcAb positive), HCV antibody (as well as HCV RNA by PCR if the subject is HCV antibody positive), and HIV.

[17] Administer 1 dose of zanubrutinib in the clinic (for the first dose only), review and dispense diary. If subjects discontinue tislelizumab but continue taking zanubrutinib, subjects are allowed to reduce visits after 1 year to every 2 months.

[18] Tumor assessments must be performed at screening, and then in conjunction with overall disease response assessments within 7 days of the end of every 4 cycles, and at disease progression. Assessments by PET-CT scan with IV contrast of neck, chest, abdomen, and pelvis and any other disease sites for non-Hodgkin lymphoma classifications that are reliably FDG-avid (includes MCL, FL, DLBCL, transformed FL, Richter's transformation, and CNS lymphomas) must be performed at Screening, Cycles 4, 8, and 12, and at suspected PD or CR. After Cycle 12, standalone CT scans will be performed every 4 cycles. Screening findings will determine whether patients are followed with PET-CT-based or CT-based assessments on study. (Refer to Section 7.2.4.)

[19] Tumor assessment including imaging scan required at a minimum of every 6 months, otherwise assessment via physical exam is acceptable.

[20] A bone marrow examination must be performed at screening for all subjects and within 7 days of the end of Cycle 4 for subjects with baseline marrow disease. In those subjects who had evidence of bone marrow disease at the time of enrollment, upon achieving a possible CR (eg, physical exam or CT scan indicating a possible CR), a bone marrow aspirate and biopsy will be obtained to confirm the CR. Additional bone marrow examinations may be performed at the investigator's discretion. Peripheral blood and/or bone marrow aspirate/biopsy with flow cytometry assessment(s) for minimal residual disease should be done 3 months after evidence of CR in all of the response parameters (i.e., hematology, CT scan).

[21] Overall disease response assessment will utilize components and guidelines specified per disease type in Appendix 4. They should accompany tumor assessments by imaging (CT, PET, etc.) as applicable.

[22] For subjects that enter efficacy follow-up, response assessments should be conducted every 3 months to identify potential progression. These response assessments may utilize physical examination rather than imaging provided an assessment utilizing imaging is conducted at least every 6 months.
[23] Subjects with CLL should have a blood sample sent at screening for interphase FISH for chromosomal abnormalities including 17p-, 11q-, 13q- and +12. Other analysis including IgVH and P53 mutational status is optional.
[24] Blood for anti-tislelizumab antibodies should be collected within 2 hours before start of Day 8 infusion on Cycle 1, Day 1 on Cycles 2, 4, 6, and every 4 cycles starting with Cycle 8 (Day 1), and also collected at the mandatory safety follow-up visit. In subjects who discontinue study therapy before 6 months, every effort should be made to analyze anti-tislelizumab antibodies approximately 6 months after the first dose. Corresponding tislelizumab PK samples will be collected at the same time when the ADA samples are collected to assess the neutralizing capacity of ADA. Analysis will be performed by a central laboratory.
[25] Subjects with an accessible tumor lesion must agree to a fresh tumor biopsy at screening and another before drug administration on Cycle 1 Day 8 (unless deemed clinically unsafe), ideally taken from the same tumor lesion, for the biomarker analysis (up to the first 12 qualified subjects). Subjects with DLBCL must have archival tumor tissues or agree to a fresh tumor biopsy for the confirmation of the DLBCL subtype. [redacted]. Optional biopsy will also be taken at the safety follow up visit for the subjects who have confirmed disease progression during the study from accessible tumor sites to obtain samples to explore resistance mechanism.
[26] Serial PK blood samples will be collected at the time points specified in Table 4-3. Procedures for collection of samples are described in the lab manual. In addition, corresponding tislelizumab PK samples will be collected at the same time when the ADA samples are collected to assess the neutralizing capacity of ADA.
[27] Patients who are suspected or known to have serious respiratory concurrent illness or who exhibit significant respiratory symptoms unrelated to underlying cancer will also take a pulmonary function test, which may include, but is not limited to, spirometry and assessment of diffusion capacity done during the Screening period to assist the determination of suitability for enrollment into the study (Refer to Section 7.1.2.
[28] Eye exam, visual acuity test, and optical coherence tomography (or equivalent diagnostic test for retinal examination) captured as standard of care prior to obtaining written informed consent and within 28 days of study drug initiation may be used rather than repeating tests. Eye exam, visual acuity test, and optical coherence tomography (or equivalent diagnostic test) will be assessed at the Screening Visit. Patients will undergo repeat assessments approximately every 15 weeks (± 7 days).
[29] The ophthalmologic assessments including eye exam, visual acuity test, and optical coherence tomography (or equivalent diagnostic test) should only be performed once at either the EOT or during safety follow up, within 30 days of study treatment end.

Table 10-2 Schedule of Assessments (Dose Expansion)

	Screening[1]	Treatment Period[2]			Safety Follow-up[3]	Efficacy Follow-up[4]	Survival Follow-up[5]
		Cycle 1 (21 days)		Cycle 2 Through Last Cycle (21 days)			
Days Window	**-28 to -1**	**D1**	**D8**	**D1 ± 3**	**30 ± 3 Days After Last Dose (Telephone Contacts 60 & 90 ± 14 Days After Last Dose)**	**Every 3 Months ±7 Days**	**Every 3 Months ±7 Days**
Informed consent	X						
Inclusion/exclusion criteria	X						
Demographic/medical history	X						
Vital signs/weight[6]	X	X	X	X	X	X	
B symptoms[7]	X	X		X	X	X	
Complete physical examination[8]	X						
Targeted physical examination[8]		X	X	X	X	X	
ECOG performance status	X	X		X	X		
Echocardiogram or MUGA	X						
12-lead ECG[9]	X	X		X	X		
Review AEs and concomitant medications[10]	X	X	X	X	X		
Hematology[11]	X	X	X	X	X	X	
Clinical chemistry[12]	X	X	X	X	X	X	
Coagulation parameters	X	X		X	X		
Urinalysis[13]	X	X	X	X	X		
Pregnancy test[14]	X	X		X			
Thyroid function[15]	X			X	X		
IgA, IgG, IgM level[16]	X			X	X	X	
Viral serologies[17]	X						
Tislelizumab administration (30 to 60 minutes infusion)[18]		X		X			
Zanubrutinib administration[19]		Orally every day					
Tumor assessment by CT scan[20]	X	Every 4 cycles			X	X[21]	
MRI with gadolinium or CT with contrast of brain[22]	X	End of Cycles 2, 4, 6, 8, 10, 12, 14, and 16					
Lumbar puncture and/or Ommaya	X	End of Cycles 2, 4, 6, 8, 10, 12, 14, and 16			X		

	Screening[1]	Treatment Period[2]			Safety Follow-up[3]	Efficacy Follow-up[4]	Survival Follow-up[5]
		Cycle 1 (21 days)		Cycle 2 Through Last Cycle (21 days)			
Days Window	**-28 to -1**	**D1**	**D8**	**D1 ± 3**	**30 ± 3 Days After Last Dose (Telephone Contacts 60 & 90 ± 14 Days After Last Dose)**	**Every 3 Months ±7 Days**	**Every 3 Months ±7 Days**
tap[23]							
[redacted] PK during lumbar puncture or Ommaya tap (optional)[23]		End of Cycles 2, 6 and 12					
Ultrasound of testicles[24]	X	Repeat at suspected CR or CRu defined in Appendix 4 for SCNSL					
Mammogram of bilateral breast[24]	X	Repeat at CR or CRu defined in Appendix 4 for SCNSL					
Ocular assessment for CNS lymphoma cohort (PCNSL and SCNSL) [25]	X	End of Cycles 4, 8, 12, and 16 for those with abnormality at Screening, and at suspected CR or CRu defined in Appendix 4					
Bone marrow evaluation[26]	X	• End of Cycle 4 • To confirm CR (at any time, Cycle 4 or later)					
Overall disease response[27]		Every 4 cycles				X[28]	
Survival status							X
Anti-tislelizumab antibodies[29]		X		X[30]	X		
Archival tumor tissues[31]	X						
Fresh tumor tissues[31]	X				X		
PK blood sampling[32]		X		X			
Pulmonary function tests[33]	X						
Optical coherence tomography (or equivalent diagnostic test) and visual acuity tests[34, 35]	X			X	X		

ADA = anti-drug antibody; D = day; AE = adverse event; ALT = alanine aminotransaminase; AST = aspartate aminotransaminase; CLL = chronic lymphocytic leukemia; CR = complete response; CRu = complete response unconfirmed; CT = computed tomography; DLBCL = diffuse large B-cell lymphoma; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence in situ hybridization; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IgVH – immunoglobin variable region heavy chain; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; MUGA = multigated acquisition scan; PCNSL = primary central nervous system (CNS) lymphoma; PCR = polymerase chain reaction; PD-1 = Programmed cell death-1; PD-L1 = Programmed Death Ligand-1;

PD-L2 = Programmed Death Ligand-2; PET = positron emission tomography; PK = pharmacokinetic; QTc = corrected QT wave; RNA = ribonucleic acid; SCNSL = secondary CNS lymphoma; TSH = thyroid stimulating hormone; WBC = white blood cell.
Assessments scheduled on study drug administration days should be performed predose, unless otherwise specified.
[1] Performed within 28 days prior to Day 1. Assessments that are performed as standard of care assessments may be used for screening.
[2] The maximum duration of treatment will be until disease progression.
[3] Performed within 30 days after the last dose of zanubrutinib (± 3 days). If the patient continues on single-agent tislelizumab, a second safety follow-up should be performed 30 days after last dose of tislelizumab. Telephone contacts with patients should be conducted to assess AEs and concomitant medications (if appropriate, ie, associated with an AE or is a new anticancer therapy) at 60, and 90 days (±14 days) after the last dose of tislelizumab.
[4] Efficacy follow-up will apply only to subjects who discontinue study drug due to reasons other than disease progression. They will remain on study and should follow the guidance provided in Section 7.5.
[5] Once subjects progress or start the use of alternative anti-cancer therapy, subjects only need to establish survival status and are not required to come in for a visit (telephone call, medical records, etc.).
[6] Vital sign time points for PK sampling will be obtained per Table 4-4.
[7] Unexplained weight loss > 10% over previous 6 months, fever (>38°C), and/or drenching night sweats.
[8] Complete physical exam includes all systems described in the body of the protocol. Targeted physical exams should be limited to systems of clinical relevance (i.e. cardiovascular, respiratory, lymph nodes, liver, and spleen) and those systems associated with clinical signs/symptoms.
[9] Perform a 12-lead ECG in triplicate at screening and at the treatment completion/early termination visit. ECG time points for PK sampling will be obtained as per Table 4-4. Additional ECGs may be required if there is a prolongation of QT or QTc, see Section 7.2.3.
[10] AEs will be recorded from the time of the first dose and all SAEs will be collected after informed consent has been signed but prior to administration of the study drug. Telephone contacts with patients should be conducted to assess AEs and concomitant medications (if appropriate, ie, associated with an AE or is a new anticancer therapy) at 60, and 90 days (±14 days) after the last dose of tislelizumab. All AEs and SAEs, regardless of relationship to study drug, will be recorded until up to 90 days after the last dose of study drug. Beyond the safety follow up period, all drug-related SAEs will be recorded by investigator until patient death, or lost to follow up, whichever occurs first
[11] Hematology, including hemoglobin, reticulocyte count, WBC count, absolute differential count (neutrophils, eosinophils, lymphocytes) and platelet count. In the event of neutropenia (absolute neutrophil count $< 1.0 \times 10^9$/L) or thrombocytopenia (platelets count $< 50 \times 10^9$/L), assessments will be performed as frequent as the physician feels needed until toxicity resolves to ≤ Grade 2. Results of blood tests taken within 24 hours may be used to allow the investigator to make the decision to proceed with dosing; in these cases, a separate pre-treatment sample must still be taken
[12] Clinical chemistry includes sodium, potassium, chloride, bicarbonate (total CO_2), glucose, urea, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, ALT, AST, LDH, alkaline phosphatase and uric acid. In the event of ≥ Grade 3 clinical chemistry toxicity, these assessments will be conducted as frequent as the physician feels needed until toxicity resolves to ≤ Grade 2. Results of blood tests taken within 24 hours may be used to allow the investigator to make the decision to proceed with dosing; in these cases, a separate pre-treatment sample must still be taken
[13] Collect urine dipstick, as well as urine microscopy, if dipstick is abnormal. If urine protein is ≥2+ by dipstick, a 24-hour urine test for total protein and a random urine test for total protein and creatinine will be obtained and evaluated on the first occasion; subsequent need for 24-hour collection will be determined by the investigator.
[14] All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening. Laboratory-based highly sensitive pregnancy tests (urine or serum) will be performed at specified subsequent visits and continued every 4 weeks (locally is acceptable) for at least 90 days after the last dose of study drug. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
[15] T3, T4, TSH; at screening, then every other cycle starting from Cycle 2, and at the mandatory safety follow-up visit. Additional T3, T4 and TSH may be performed at the discretion of the investigator.
[16] IgA, IgG and IgM tests should be performed for all subjects at screening and only for those with significant abnormal findings at subsquent visits.
[17] Viral serologies include hepatitis B (HBsAg and total HB core antibody [anti-HBc] as well as HBV DNA by PCR if the subject is HBcAb positive), Hepatitis C virus (HCV) antibody (as well as HCV RNA by PCR if the subject is HCV antibody positive), and HIV.
[18] For Cohort 4A, subjects will not receive the combination dosing of zanubrutinib and tislelizumab until Cycle 5.
[19] Administer 1 dose of zanubrutinib in the clinic (for the first dose only), review and dispense diary. If subjects discontinue tislelizumab but continue taking zanubrutinib, subjects are allowed to reduce visits after 1 year to every 2 months.

[20] Tumor assessments for subjects with non-CNS lymphoma must be performed at screening, and then in conjunction with overall disease response assessments within 7 days of the end of every 4 cycles, and at disease progression. Assessments by PET-CT scan with IV contrast of neck, chest, abdomen, and pelvis and any other disease sites for non-Hodgkin lymphoma classifications that are reliably FDG-avid (includes MCL, FL, DLBCL, transformed FL, Richter's transformation, and CNS lymphomas) must be performed at Screening, Cycles 4, 8, and 12, and at suspected PD or CR. After Cycle 12, standalone CT scans will be performed every 4 cycles. Screening findings will determine whether patients are followed with PET-CT-based or CT-based assessments on study. (Refer to Section 7.2.4.). For the early termination visit, CT is required if the previous scan was performed more than 3 months ago. Cycle 1, Day 1 laboratory assessments should be considered baseline.

[21] Tumor assessment including imaging scan required at a minimum of every 6 months, otherwise assessment via physical exam is acceptable.

[22] Only for subjects with PCNSL or SCNSL of breast or testicular origin (Cohort 4 of expansion part). MRI of gadolinium is preferred imaging modality. CT with contrast of brain may be substituted if contraindication to MRI (e.g. implanted metal or electronic device like pacemaker, insulin pump, claustrophobia).

[23] Cerebrospinal fluid will be obtained by lumbar puncture and/or Ommaya tap in subjects with PCNSL or SCNSL of breast or testicular origin only (Cohort 4 of Expansion part), and will include cytology, total cell count, protein level, and glucose level. Lumbar puncture should only be performed in subjects with PCNSL or SCNSL of breast or testicular origin who are not at risk of herniation. Cerebrospinal fluid analyses are required after Screening only if these studies were initially positive at Screening or if clinically indicated by new symptoms or signs. Patients with significant CSF abnormalities at baseline, are required to have both repeat lumbar puncture and Ommaya tap at suspected CR or CRu defined per Appendix 4. CSF fluid needs to be analyzed at the site local pathology laboratory. If subjects have CSF collected for disease assessment (post treatment) above, it is recommended to spare 2 mL of CSF for drug measurements (especially at Cycle 2). In this case, at end of Cycles 2, 6 and 12, subjects will take the morning dose of zanubrutinib at the clinic, and CSF collection will be performed around 2 hours (+/- 10 minutes) following zanubrutinib dose for measurement of zanubrutinib and tislelizumab concentration in CSF. On the same day of CSF collection, blood samples for measuring blood zanubrutinib and serum tislelizumab concentrations will be collected at pre-dose (prior to zanubrutinib dose) and at 2 hours (+/- 10 minutes) post zanubrutinib dose. CSF collection for PK samples is optional.

[24] Testicular ultrasound required only for male subjects with SCNSL of testicular origin and only if the PET/CT is positive for testicular disease. Bilateral mammogram required only for male or female subjects with SCNSL of breast origin. Repeat testicular ultrasound or bilateral breast mammogram required at suspected CR or CRu defined per for PCNSL or SCNSL.

[25] For PCNSL and SCNSL (Cohorts 4A and 4B), ophthalmologic examination includes a complete examination with dilated fundus and slit-lamp examinations. Color photography of the posterior pole should be obtained in those patients with ocular involvement. Fluorescein angiography may be helpful to confirm lymphomatous involvement of the retina.

[26] A bone marrow examination must be performed at screening for all subjects and within 7 days of the end of Cycle 4 for subjects with baseline marrow disease. In those subjects who had evidence of bone marrow disease at the time of enrollment, upon achieving a possible CR (e.g. physical exam or CT scan indicating a possible CR), a bone marrow aspirate and biopsy will be obtained to confirm the CR. Additional bone marrow examinations may be performed at the investigator's discretion. Peripheral blood and/or bone marrow aspirate/biopsy with flow cytometry assessment(s) for minimal residual disease should be done at least 3 months after the last dose if there is evidence of CR in all of the response parameters (i.e., hematology, CT scan).

[27] Overall disease response assessment will utilize components and guidelines specified per disease type in Appendix 4. They should accompany tumor assessments by imaging (CT, PET, etc.) as applicable.

[28] For subjects that enter efficacy follow-up, response assessments should be conducted every 3 months to identify potential progression. These response assessments may utilize physical examination rather than imaging, provided an assessment utilizing imaging is conducted at least every 6 months.

[29] Blood for anti- tislelizumab antibodies should be collected within 2 hours before start of Day 1 infusion on Cycles 1, 2, 5, 9, and 17, and also collected at the mandatory Safety Follow-Up Visit. In subjects who discontinue study therapy before 6 months, every effort should be made to analyze anti-tislelizumab antibodies approximately 6 months after the first dose. Corresponding tislelizumab PK samples will be collected at the same time when the ADA samples are collected to assess the neutralizing capacity of ADA. Analysis will be performed by a central laboratory.

[30] Collect at Day 1 of Cycles, 2, 3, 6 and every 4 cycles starting with Cycle 8 (Day 1).

[31] [redacted].

[32] Serial PK blood samples will be collected at the time points specified in Table 4-4. Procedures for collection of samples are described in the Lab Manual. In addition, corresponding tislelizumab PK samples will be collected at the same time when the ADA samples are collected to assess the neutralizing capacity of ADA.

[33] Patients who are suspected or known to have serious respiratory concurrent illness or who exhibit significant respiratory symptoms unrelated to underlying cancer will also take a pulmonary function test, which may include, but is not limited to, spirometry and assessment of diffusion capacity done during the Screening period to assist the determination of suitability for enrollment into the study. (Refer to Section 7.1.2.)

[34] Eye exam, visual acuity test, and optical coherence tomography (or equivalent diagnostic test for retinal examination) captured as standard of care prior to obtaining written informed consent and within 28 days of study drug initiation may be used rather than repeating tests. Eye exam, visual acuity test, and optical coherence tomography (or equivalent diagnostic test) will be assessed at the Screening Visit. Subjects will undergo repeat assessments approximately every 15 weeks (± 7 days). For subjects with PCNSL or SCNSL (Cohorts 4A and 4B), eye examinations performed for response evaluation do not need to be duplicated if they fall within the acceptable scheduling window for the eye exam, visual acuity test, and optical coherence tomography.

[35] The ophthalmologic assessments including eye exam, visual acuity test, and optical coherence tomography (or equivalent diagnostic test) should only be performed once at either the EOT or during safety follow up, within 30 days of study treatment end. (Refer to Section 7.2.7.)

10.1.1 A Brief summary of efficacy assessments' frequencies

	On-treatment	Efficacy follow-
Dose escalation		
Tumor by CT	Every 4 cycles (12 weeks)	Every 3 months
Bone marrow evaluation	Every 4 cycles (12 weeks)	
Overall disease response	Every 4 cycles (12 weeks)	Every 3 months
Dose expansion		
Tumor by CT	Every 4 cycles (12 weeks)	Every 3 months
Disease specific assessments		
MRI with gadolinium/ CT with contrast	Every 2 cycles (6 weeks till end of cycle 16 [48 wks])	
Lumbar puncture and/or Ommaya tap	Every 2 cycles (6 weeks till end of cycle 16 [48 wks])	
Ultrasound of testicles	Repeat at suspected CR/Cru for SCNSL?	
Mammogram of bilateral breast	Repeat at suspected CR/Cru for SCNSL?	
Ocular assessment for CNS lymphoma cohort	Every 4 cycles till cycle 16 [48 weeks] for those with abnormality at screening, and at suspected CR/CRu	
Bone marrow evaluation	Every 4 cycles (12 weeks)	
Overall disease response	Every 4 cycles (12 weeks)	Every 3 months
OS	Every 3 months	Every 3 months

10.2 RESPONSE CRITERIA

Per Protocol Appendix 4. Note: increases and decreases are relative to baseline unless otherwise indicated.

10.2.1 CHRONIC LYMPHOCYTIC LEUKEMIA

Response*	Group A			Group B	Bone Marrow‡
	Lymphadenopathy†	**Physical Exam (Liver, Spleen)**	**Blood lymphocytes**	**Peripheral Blood**	
CR	None > 1.5 cm	Normal	< 4 x 10^9/L	Platelets > 100 x 10^9/L Hemoglobin > 11.0 g/dL ANC > 1.5 x 10^9/L	Normocellular, < 30% lymphocytes No B-lymphoid nodules, hypocellular marrow defines CRi*
CRi	None > 1.5 cm	Normal	< 4 x 10^9/L	Persistent anemia, thrombocytopenia, or neutropenia related to drug toxicity	
PR	Decrease ≥ 50% in lymphadenopathy	Decrease ≥ 50% in spleen or liver enlargement	< 5 x 10^9/L OR Decrease ≥ 50%	Platelets > 100 x 10^9/L or ≥ 50% improvement over baseline OR Hemoglobin > 11.0 g/dL or >50% improvement over baseline OR ANC > 1.5 x 10^9/L or > 50% improvement over baseline	50% reduction in marrow infiltrate
PRL	Decrease ≥ 50% in lymphadenopathy	Decrease ≥ 50% in spleen or liver enlargement	Decrease < 50% or increase from baseline	Platelets > 100 x 10^9/L or 50% improvement over baseline OR Hemoglobin > 11.0 g/dL or 50% improvement over baseline OR ANC > 1.5 x 10^9/L or > 50% improvement over baseline	50% reduction in marrow infiltrate, or B-lymphoid nodules
SD	Absence of PD and failure to achieve at least a PR				

PD**	Increase ≥ 50% in lymphadenopathy from nadir OR new lesion	Increase ≥ 50% in splenomegaly OR Increase ≥ 50% in hepatomegaly	Not assessed	Platelets decrease ≥ 50% from baseline secondary to CLL OR Hemoglobin decrease of > 2 g/dL from baseline secondary to CLL	

Abbreviations: ANC = absolute neutrophil count; CLL = chronic lymphocytic leukemia; CR = complete remission (response); CRi = CR with incomplete bone marrow recovery; PD = progressive disease; PR = partial remission (response); PRL = partial remission (response) with lymphocytosis; SD = stable disease.

Group A criteria define the tumor load, group B criteria define the function of the hematopoietic system (or marrow).

*CR: all of the criteria have to be met, and patients have to lack disease-related constitutional symptoms; PR: at least 2 of the criteria of group A (lymphadenopathy, splenomegaly, hepatomegaly, or lymphocytes) plus 1 of the criteria of group B (platelets, hemoglobin, or ANC) have to be met; PRL: presence of lymphocytosis, plus ≥ 50% reduction in lymphadenopathy and/or in spleen or liver enlargement, plus 1 of the criteria for platelets, hemoglobin, or ANC have to be met; SD: is absence of PD and failure to achieve at least a PR; PD: at least 1 of the above PD criteria has to be met.
**Note: Isolated elevation of treatment-related lymphocytosis by itself will not be considered PD unless patient becomes symptomatic as a result from this per Cheson 2012.

a. Computed tomography (CT) scan of abdomen, pelvis, and thorax may be used if previously abnormal
b. Without need for exogenous growth factors
c. If the sum products of ≤ 6 lymph nodes or in the largest diameter of the enlarged lymph node(s) detected before therapy and no increase in any lymph node or new enlarged lymph nodes

† Sum of the products of multiple lymph nodes (as evaluated by CT scans, or by physical examination)
‡ These parameters are irrelevant for some response categories

References:
Cheson BD, Byrd JC, Rai KR, et al. Novel targeted agents and the need to refine clinical end points in chronic lymphocytic leukemia. J Clin Oncol 2012;30:2820-2.
Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood 2008;111:5446-5.

Group A criteria define the tumor load, group B criteria define the function of the hematopoietic system (or marrow).
* CR (complete remission): all of the criteria have to be met, and subjects have to lack disease-related constitutional symptoms; PR (partial remission): at least 1 of the criteria of group A plus 1 of the criteria of group B have to be met (Persistent lymphocytosis should not interfere with the time of designation of a PR, which should be based more on the other measurable aspects of the disease than on lymphocytosis.) ; SD is absence of progressive disease (PD) and failure to achieve at least a PR; PD: at least 1 of the above criteria of group A or group B has to be met.
† Sum of the products of multiple lymph nodes (as evaluated by CT scans in clinical trials, or by physical examination in general practice).
‡ These parameters are irrelevant for some response categories.
CRi (CR with incomplete bone marrow recovery): Fulfills all requirements for CR except has persistent neutropenia, anemia, or thrombocytopenia thought to be unrelated to the disease and likely related to drug toxicity. These subjects must have a normal bone marrow aspirate and biopsy with no evidence of clonal infiltrates.
Nodular PR: Persistent bone marrow nodules on bone marrow biopsy in subjects achieving a CR or PR. Lymphoid aggregates should be evaluated with immunohistochemistry to determine whether they are comprised of CLL cells, lymphocytes other than CLL cells, or T cells.

10.2.2 NON-HODGKIN LYMPHOMA (including SLL)

Response assessment will be performed according to the 2014 International Working Group in Non-Hodgkin's Lymphoma (NHL) criteria (Lugano classification).

Positron emission tomography-computed tomography (PET-CT) should be used for response assessment in fluorodeoxyglucose (FDG)-avid histologies (using the 5-point scale provided in the footnote of the table); computer tomography (CT) is preferred for low or variable FDG avidity.

Response and site	PET-CT-Based Response (Patients with PET-Avid Disease at Screening)	CT-Based Response (Patients without PET-Avid Disease at Screening)
Complete	**Complete metabolic response**	**Complete radiologic response (all of the following)**
Lymph nodes and extralymphatic sites	Score 1, 2, or 3[a] with or without a residual mass on 5-point scale [b] It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow leg (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete mediastinum response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.	Target nodes/nodal masses must regress to ≤1.5 cm in LDi No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if inderterminate, IHC negative
Partial	**Partial metabolic response**	**Partial remission (all of the following)**
Lymph nodes and extralymphatic sites	Score 4 or 5[b] with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value When no longer visible, 0 x 0 mm For a node >5 mm x 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesion	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal

New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	**No metabolic response**	**Stable disease**
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	<50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesion	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease**	**Progressive metabolic response**	**Progressive disease requires at least 1 of the following:**
Individual target nodes/nodal masses Extranodal lesions	Score 4 or 5 with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	PPD progression: An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions> 2 cm In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If not prior splenomegaly, must increase by at least 2 cm from baseline
		New or recurrent splenomegaly
Nonmeasured lesion	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extra nodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size

		unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: CT = computed tomography; FDG = fluorodeoxyglucose; IHC = immunohistochemistry; LDi = longest transvers diameter of a lesion; MRI = magnetic resonance imaging; PET = positron emission tomography; PPD = cross product of the LDi and perpendicular diameter; SDi = shortest axis perpendicular to the LDi; SPD = sum of the product of the perpendicular diameters for multiple lesions.

a A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs). GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow). FDG uptake may be greater than the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

b PET 5-point scale:
1 = no uptake above background; 2 = uptake ≤ mediastinum; 3 = uptake > mediastinum; 4 = uptake moderately > liver; 5 = uptake markedly higher than liver and/or new lesions; X = new areas of uptake unlikely to be related to lymphoma.

non-Hodgkin lymphoma

10.2.3 HAIRY CELL LEUKEMIA (HCL)

Response Criteria

- Complete response (CR) is defined as the absence of hairy cells from the peripheral blood and bone marrow along with resolution of organomegaly and cytopenia. In CR immunohistochemistry reveals no clustering (≥ 3 cells) of CD20-positive or DBA.44-positive cells.
- Partial response (PR) is defined as a normalization of cytopenia along with a minimum 50% improvement in both organomegaly and bone marrow infiltration with no circulating hairy cells.

Consensus resolution: proposed criteria for evaluation of response to treatment in hairy cell leukemia (Author anonymous). Leukemia. 1987;1:405.

10.2.4 CNS LYMPHOMAS (PCNSL and SCNSL) Response Criteria

Radiographic Response Assessment

Radiographic criteria will be assessed using gadolinium-enhanced magnetic resonance imaging (MRI) of brain (contrast-enhanced CT may be substituted in patients in whom MRI is medically contraindicated), in accordance with the criteria developed in the International Workshop to Standardize Baseline Evaluation and Response Criteria in Primary CNS Lymphoma.[22] Thorough evaluation to determine full extent of disease in subjects with PCNSL or SCNSL is critical and includes whole body PET/diagnostic CT scan with contrast (refer to Table 4-2). Whole body PET/diagnostic CT will be required at screening, and if positive, at specified timepoints during study treatment, to evaluate for presence of extra-CNS disease in PCNSL and primary site disease (i.e., breast or testes) in SCNSL. Response criteria will be assessed in accordance with the Lugano Classification (Cheson et al, 2014).

Ocular Response Assessment

A detailed ophthalmologic examination with dilated fundus examination and slit-lamp examination should be done to exclude vitreous, retinal, or optic nerve involvement. Fluorescein angiography may be helpful to confirm lymphomatous involvement of the retina. Color photography of the posterior pole of the eye should be obtained in those patients with ocular involvement to follow and document response to therapy.

CSF Cytology Assessment

Cerebrospinal fluid will be obtained by lumbar puncture and/or Ommaya tap, and will include cytology, total cell count, protein level, and glucose level. Total protein has been identified as an important prognostic factor and should be analyzed in all patients. Ideally, CSF protein levels should be assessed on lumbar puncture samples because ventricular CSF has a lower normal value. Lumbar puncture though should only be performed in subjects who are not at risk of herniation. Cerebrospinal fluid analyses are required after screening only if these studies were initially positive at screening or if clinically indicated by new signs/symptoms, or to confirm CR or CRu.

Response	Whole Body Imaging	Brain Imaging	Corticosteroid Dose[b]	Eye Examination[c]	CSF Cytology[d]
CR	Refer to Lugano criteria provided above for NHL response on CR status	No contrast enhancement	None	Normal	Negative
CRu		No contrast enhancement	Any	Normal	Negative
		Minimal abnormality	Any	Minor RPE abnormality	Negative
PR[e]	Refer to	50% decrease in	Irrelevant	Minor RPE	Negative

	Lugano criteria provided above for NHL response on PR status	enhancing tumor		abnormality or normal	
		No contrast enhancement	Irrelevant	Decrease in vitreous cells or retinal infiltrate	Persistent or suspicious
SD	Refer to Lugano criteria provided above for NHL response on No Response or SD status	Does not meet conditions specified in responses or PD; defined as less than a PR but is not PD			
PD[f]	Refer to Lugano criteria provided above for NHL response on PD status	25% increase in lesion	Irrelevant	Recurrent or new ocular disease	Recurrent or positive
		Any new site of disease: central nervous system or systemic			

CR: complete response; CRu: unconfirmed complete response; NHL = non-Hodgkin lymphoma; RPE: retinal pigment epithelium; PR: partial response; SD: stable disease; PD: progressive disease

1. a Repeat testicular ultrasound for male subjects or bilateral breast mammogram for female or male subjects are required at suspected CR or CRu for SCNSL only.
2. b At the time a CR is determined, the patient should have discontinued use of all corticosteroids for ≥ 2 weeks (rare exceptions may be made for those receiving corticosteroids for another diagnosis).
3. c All CRs should be confirmed by repeat imaging; CR in the eyes should be confirmed by repeat evaluation.
4. d In the setting of primary leptomeningeal disease, PR is not recognized; all patients should be categorized as CR, CRu, SD, or PD.
5. e For subjects with PCNSL or SCNSL, repeat lumbar puncture and Ommaya tap are both required at suspected CR or Cru or if clinically indicated by new symptoms or signs.

f For classification of PD, confirmation of any of the listed conditions would qualify as having met PD criteria.

10.3 DEFINITION OF DLT

Note that per protocol section 4.1.1, a DLT is a toxicity or adverse event (AE) occurring during the DLT assessment period (21 days from Cycle 1 Day 8 to Cycle 1 Day 28), which cannot be primarily attributed to a cause other than zanubrutinib and/or tislelizumab (such as disease progression, underlying illness, concurrent illness, or concomitant medication) and meets 1 of the following criteria:

1) Nonhematologic Grade 4 (or Grade 3 lasting > 3 days) toxicity excluding:
    a. Laboratory abnormalities deemed by investigators as being not clinically important
    b. Grade 3 tumor flare
    c. Grade 3 infusion-related event that resolves to Grade 1 within 21 days
    d. Grade 3 nausea or vomiting
    e. Grade 3 hypertension
2) Grade 4 neutropenia lasting > 7 days, not attributable to active leukemia or lymphoma
3) Grade 4 thrombocytopenia lasting > 7 days, not attributable to active leukemia or lymphoma
4) Any toxicity that requires drug hold of 1 or both investigational agents for more than 2 weeks

10.4 MISSING DATA IMPUTATION RULE

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.

10.4.1 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 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.

10.4.2 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 and year = year of treatment start date, then set to treatment start date
- If both month and day are missing and year ≠ year of treatment start date, then set to January 01
- If day is missing and month and year = month and year of treatment start date, then set to treatment start date
- If day is missing and month and year ≠ month and year of treatment start date, then set to first day of the month
- If start date is completely missing, set to treatment start date as long as adverse event end date is not before treatment start date

If end date of an adverse event 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.

10.4.3 Deaths

In case only the day of a death date is missing, the death will be assumed to be on the 1st date of the month if the last date of subject known to be alive is earlier that the 1st date of the month, otherwise the death date will be assumed to be on 1 day after the last date of subject known to be alive.

10.4.4 Date of diagnosis or date of progression to most recent prior therapy

When the date of diagnosis or date of progression to most recent prior therapy is partially missing, the date will be imputed to calculate time from diagnosis and time from most recent progression. The following rules will be applied to impute partial dates:

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 of the month

10.5 CLINICAL LABORATORY ASSESSMENTS

Clinical Chemistry	Hematology	Coagulation	Urinalysis	Immunoglobulin Assessment and Thyroid Testing	Cerebrospinal fluid[b]
Alkaline phosphatase ALT AST Albumin Bicarbonate (Total CO_2) Calcium Chloride Creatinine Glucose LDH Magnesium Phosphorus Total protein Potassium Sodium Total and direct bilirubin Urea Uric acid	Hemoglobin Reticulocyte count Platelet counts WBC count with differential Neutrophil count Bands (optional) Lymphocyte count Eosinophil count	Prothrombin time Partial thromboplastin time International normalized ratio	pH Specific gravity Glucose Protein Ketones Blood 24-hour protein[a] Random urine protein to creatinine ratio[a]	IgA IgG IgM T3 T4 TSH	Cell count Total protein Glucose Cytology