Clinical Study Protocol

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**

Protocol Number: **BGB-3111_BGB-A317_Study_001**

Date of Protocol: **Original: Version 1.0, 25 January 2016**

Amendment: Version 2.0, 7 November 2016

Amendment: Version 3.0, 28 June 2017

Amendment: Version 4.0, 15 March 2018

Amendment: Version 5.0, 02 May 2019

Study Phase: **1b**

Sponsor: **BeiGene Aus Pty Ltd**
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Sponsor Medical Monitor: [redacted]

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[redacted] **Date**

Sponsor Medical Monitor

PROTOCOL AMENDMENT 5.0 - AMENDMENT RATIONALE

Rationale:
This protocol is being amended to include the following major changes:

- Changed all references to "Safety Population" to "Safety Analysis Set." Text revised as correction and for consistency with other BeiGene protocols.
- Deleted text regarding which version of Statistical Analysis Program is used. Text is more appropriately documented in the SAP.
- Removal of QT interval prolongation medications. The BGB-3111-106 study was recently completed in healthy volunteers and has shown that both therapeutic and supratherapeutic doses of zanubrutinib had no clinically relevant effect on ECG parameters, including QTc intervals.
- Added results of drug-drug interaction study.
- Closed Cohort 4A to enrolment due to the dosing schedule not being ideal for decreasing tumor burden rapidly as BTK-inhibition is not initiated until the 5th cycle, according to investigator feedback, and opened Cohort 4B immediately.

In addition, administrative updates (eg, adding abbreviations, correcting numbering in numbered lists), corrections of minor typographical and formatting errors, editorial changes, and/or style and formatting revisions have been made to improve clarity and consistency throughout the document.

SYNOPSIS

Name of Sponsor/Company:	**BeiGene Aus Pty Ltd**
Name of Finished Product:	**Zanubrutinib (BGB-3111) and Tislelizumab (BGB-A317)**
Name of Active Ingredient:	Zanubrutinib (a Bruton's tyrosine kinase [BTK] inhibitor) and tislelizumab (a humanized anti-programmed death-1[PD-1] monoclonal antibody)
Title of Study:	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
Protocol No:	BGB-3111_BGB-A317_Study_001
Study Centers:	10-15 study centers globally
Study duration: Screening (up to 28 days), treatment (until progression), safety follow-up (30 days), and survival follow-up (every 3 months by telephone to assess survival until death or conclusion of the study)	**Phase:** 1b

Objectives:

Primary:

- To determine the maximum tolerated dose (MTD) and/or the recommended Phase 2 dose (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 tislelizumab and zanubrutinib (Cohort 4A) in previously treated subjects with B-cell malignancies.

Secondary:

- 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 pharmacokinetics (PK) of zanubrutinib and tislelizumab when administered in combination.
- To assess host immunogenicity to tislelizumab when administered in combination with zanubrutinib.

Exploratory:

[redacted]

Methodology:

This is a Phase 1b study to evaluate safety, tolerability, and preliminary efficacy of zanbrutinib in combination with tislelizumab in subjects with B-cell malignancies, including relapsed/refractory chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), mantle cell lymphoma (MCL), non-germinal center B-cell (non-GCB) diffuse large B-cell lymphoma (DLBCL), GCB DLBCL, follicular lymphoma (FL), marginal zone lymphoma (MZL), hairy cell leukemia (HCL), transformed FL, Richter's transformation, primary central nervous system lymphoma (PCNSL), and secondary CNS lymphoma (SCNSL) of breast or testicular origin (Note: WM subjects are excluded from enrollment as of Amendment 3). The study is divided into dose escalation and a dose expansion.

Study Treatment:

Zanubrutinib will be administered orally every 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) as described below.

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. For Amendment 5.0, Cohort 4A is being discontinued. There were no safety or tolerability signals that led to the discontinuation of Cohort 4A. Cohort 4B will be immediately activated with Amendment 5.0. As of March 2019, 3 subjects with CNSL have been enrolled in Cohort 4A; however, no subjects remain on study treatment in this cohort, which is now closed to treatment and further enrollment. For Cohort 4B, 10 subjects with PCNSL and SCNSL will receive combination zanubrutinib and tislelizumab at the RP2D defined by the dose escalation starting at Day 1 of Cycle 1 and all cycles thereafter. 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. All cycles will be 21 days.

Subjects will continue to take zanubrutinib and tislelizumab as scheduled until one of the events listed in Section 4.2.4.3 occurs.

Dose Escalation

The purpose of dose escalation is to determine the 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. DLTs are defined in Section 4.1.1. 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. ○ ≥ 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] Section 7.3.1). **Dose Escalation Safety Expansion (additional subject enrollment for Dose Levels 1, 2, and 3)** 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 (eg, 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 Safety Monitoring Committee for additional safety information (see Section 7.3.1). **Dose Expansion** In the dose expansion, there will be 4 dose expansion cohorts at the RP2D for the combination of tislelizumab and zanubrutinib (see Section 4.2.1 for the specific inclusion requirements of each cohort): • 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.
Planned Number of Subjects:	Approximately 85 subjects
Study Population	**Inclusion Criteria:** 1. Dose escalation for Dose Levels 1, 2, and 3: Subjects with relapsed or refractory World Health Organization (WHO) classification-defined B-lymphoid malignancy following at least 1 line of therapy, with no therapy of higher priority available, including CLL/SLL, MCL, FL, HCL, MZL, non-GCB DLBCL, GCB DLBCL, transformed FL, and Richter's transformation (NOTE: subjects with WM are excluded from enrollment as of Amendment 3). 2. Dose expansion for Cohorts 1 to 4: Subjects with either of the following relapsed or refractory WHO-classified lymphoid malignancies who have received at least 1 prior line of standard therapy:

	a. Cohort 1: GCB DLBCL, with cell-of-origin defined by either immunohistochemistry or gene expression profiling. b. Cohort 2: non-GCB DLBCL, with cell-of-origin defined by either immunohistochemistry or gene expression profiling. Subjects who have transformed to DLBCL from another histology will be allowed to enroll in Cohort 3. c. Cohort 3: Transformed lymphoid malignancy, including but not limited to: i. Large cell transformation of chronic lymphocytic leukemia (Richter's transformation). ii. Large cell transformation of other WHO-classified indolent non-Hodgkin lymphoma, including FL and MZL. d. Cohort 4: Histologically confirmed PCNSL or SCNSL of breast or testicular origin: i. Must be able to tolerate lumbar puncture and/or Ommaya taps ii. Must have received at least 1 prior CNS directed therapy. iii. Presence of brain parenchymal and/or leptomeningeal disease. 3. Aged ≥ 18 years, able and willing to provide written informed consent and to comply with the study protocol. 4. Measurable disease for non-Hodgkin lymphoma defined as ≥ 1 nodal lesion that is > 15 mm in the longest diameter and can be accurately measured in at least 2 dimensions with computed tomography (CT) scan, or ≥ 1 extra-nodal lesion that is > 10 mm in the longest diameter and can be accurately measured in at least 2 dimensions with CT scan, except for PCNSL or SCNSL. 5. Subjects with an accessible tumor lesion must agree to a tumor biopsy at Screening and before the drug administration on Cycle 1 Day 8, ideally taken from the same tumor lesion, for the biomarker analysis (up to first 12 qualified subjects), except for PCNSL. Additionally, subjects with DLBCL must have archival tumor tissue or agree to have a biopsy for confirmation of the DLBCL subtype. 6. Laboratory parameters as specified below: a. Hematologic: platelet count ≥ 50×10^9/L; absolute neutrophil count ≥1.0×10^9/L; subjects with neutrophils < 1.0×10^9/L unless cytopenias are a direct result of active leukemia or lymphoma, in which case platelet count ≥ 35×10^9/L, absolute neutrophil count ≥ 0.75×10^9/L are allowed. (Note: Platelet transfusion administered ≤ 7 days of screening to raise pre-treatment platelet count to ≥ 35 x 10^9/L is prohibited)

	b. Hepatic: total bilirubin ≤ 1.5 ×the upper limit of normal (ULN) or ≤ 2.0 × ULN for subjects with Gilbert syndrome, aspartate aminotransaminase (AST), and alanine aminotransaminase (ALT) ≤ 3× ULN c. Renal: creatinine clearance ≥ 30 mL/min (as estimated by the Cockcroft-Gault equation or as measured by nuclear medicine scan or 24-hour urine collection). Subjects requiring hemodialysis will be excluded. 7. Anticipated survival of at least 4 months 8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. 9. Female subjects of childbearing potential and non-sterile males must practice at least 1 of the following methods of birth control with partner(s) throughout the study and for ≥ 3 months after discontinuing study drugs: total abstinence from sexual intercourse, double-barrier contraception, intrauterine device or hormonal contraceptive initiated at least 3 months prior to first dose of study drug. 10. Male subjects must not donate sperm from initial study drug administration, until 180 days after drug discontinuation. **Exclusion Criteria:** 1. Known, active, central nervous system lymphoma or leukemia, except for Cohort 4 2. Diagnosis with Waldenstrom's macroglobulinemia (WM). 3. For PCNSL and SCNSL (Cohort 4): a. Requires corticosteroid therapy > 16 mg dexamethasone daily or equivalent b. Corticosteroid therapy ≤ 16 mg dexamethasone daily or equivalent at study entry from which, in the Investigator's opinion, it is expected that the subject cannot be tapered off after the first 4 weeks of study treatment c. Intraocular PCNSL without evidence of brain disease d. SCNSL actively receiving treatment for extra-CNS disease e. PCNSL actively receiving concomitant local or systemic therapy for CNS disease. 4. Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenia purpura 5. History of stroke or cerebral hemorrhage within 6 months of enrollment 6. History of significant cardiovascular disease, defined as:

	a. Congestive heart failure greater than New York Heart Association (NYHA) class II according to the NYHA functional classification b. Unstable angina or myocardial infarction with 6 months of enrollment c. Serious cardiac arrhythmia or clinical significant electrocardiogram (ECG) abnormality: corrected QT wave (QTcF) > 480 msec based on the Fridericia's formula or other ECG abnormalities including second-degree atrioventricular block type II, third-degree atrioventricular block. Subjects who have a pacemaker, will be allowed on study despite ECG abnormalities or the inability to calculate the QTc. 7. Severe or debilitating pulmonary disease (dyspnea at rest, significant shortness of breath, congestive obstructive pulmonary disease). 8. History of severe allergic or anaphylactic reactions to monoclonal antibody therapy. 9. Prior BTK inhibitor or anti- PD-1/ PD-L1 treatment 10. Any illness or condition that in the opinion of the investigator may affect safety of treatment or evaluation of any study endpoint. 11. Active autoimmune diseases or history of severe autoimmune diseases; these include but are not limited to a history of immune related neurologic disease, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barre syndrome, myasthenia gravis, systemic lupus erythematosus, rheumatoid arthritis, connective tissue diseases, scleroderma, inflammatory bowel disease, Crohn's disease, ulcerative colitis, autoimmune hepatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, or clinically manifest antiphospholipid syndrome. Note: Subjects are permitted to enroll if they have vitiligo, eczema, type I diabetes mellitus, or endocrine deficiencies, including thyroiditis managed with replacement hormones including physiologic doses of corticosteroids. Subjects with Sjögren's syndrome and psoriasis controlled with topical medication and subjects with positive serology, such as antinuclear antibodies, or antithyroid antibodies should be evaluated for the presence of target organ involvement and potential need for systemic treatment but should otherwise be eligible. 12. A condition requiring systemic treatment with either corticosteroids (> 20 mg daily prednisone or equivalent) or other immunosuppressive medications within 14 days of study drug administration, except for PCNSL and SCNSL. Note: adrenal replacement doses ≤ 20 mg daily prednisone or equivalent are permitted in the absence of active autoimmune disease; subjects are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). 13. History of interstitial lung disease or noninfectious pneumonitis except for that induced by radiation therapy.

	14. Requirement for medications which are strong cytochrome P450 (CYP)3A inhibitors or inducers. 15. Vaccination with a live vaccine within 28 days of the initiation of treatment. 16. A candidate for hematopoietic stem cell transplantation or have received prior autologous hematopoietic stem cell transplant within the past 6 months. Subjects are excluded if they had received prior allogeneic stem cell transplantation. 17. Participated in any investigational drug study within 28 days or not recovered from toxicity of any prior chemotherapy to Grade ≤ 1. 18. History of other active malignancies within 2 years of study entry, with the exception of adequately treated in-situ carcinoma of cervix; localized basal cell or squamous cell carcinoma of skin; or previous malignancy confined and treated locally (surgery or other modality) with curative intent. 19. Major surgery in the past 4 weeks prior to the first day of screening. 20. Active and symptomatic fungal, bacterial, and/or viral infection, human T-cell lymphotropic virus type 1 seropositive status. 21. HIV infection, or active hepatitis B (eg, hepatitis B surface antigen [HBsAg] reactive) or hepatitis C (eg, hepatitis C virus [HCV] ribonucleic acid [RNA] detected. • Hepatitis B/C serologic markers and viral load will be tested at screening. The hepatitis B testing includes HBsAg, HBcAb, and HBsAb as well as hepatitis B virus (HBV) DNA by PCR if the subject is negative for HBsAg but HBcAb positive (regardless of HBsAb status). The hepatitis C testing includes hepatitis C virus (HCV) antibody as well as HCV RNA by PCR if the subject is HCV antibody positive. Subjects with positive HBsAg and/or detectable level of HBV DNA or detectable level of HCV RNA (≥ 15 IU/mL**)** are not eligible. Subjects negative for HBsAg, HBcAb positive, and HBV DNA negative must undergo monthly HBV DNA screening by PCR. Subjects positive for HCV antibody but negative for HCV RNA (defined as <15 IU) must undergo monthly HCV RNA screening. 22. Inability to comply with study procedures. 23. Pregnant or nursing women. 24. Men or women of childbearing potential who refuse to use an adequate measure of contraception unless they have past medical history of surgical sterilization. 25. Currently taking or plan to take CNS penetrant therapy such as thiotepa, cytarabine, or partially CNS penetrant agents known to be active in lymphoid tumors such as rituximab.

	26. Has taken or plans to take any chemotherapy, immunotherapy (eg, interleukin, interferon, thymoxin) or any investigational therapies to treat leukemia or lymphoma within 28 days or 5 half-lives (whichever is shorter) of the first study drug administration, including CNS penetrating agents. Has received radiotherapy to treat leukemia or lymphoma within 21 days of the first study drug administration.
Test product, dose, and mode of administration:	Zanubrutinib: oral 80 mg capsules Tislelizumab: 10 mL/vial, 10 mg/mL Tislelizumab will be administered by intravenous (IV) infusion
Reference therapy, dose, and mode of administration:	Not applicable

Criteria for Evaluation:

Primary endpoint:

- Dose escalation: The MTD and/or 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).

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 complete response [CR] or partial response [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 progressive disease [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).
- The PK profiles of tislelizumab and zanubrutinib.
- The incidence of development of anti-drug antibody to tislelizumab when given in combination with zanubrutinib.

Exploratory endpoints:

- [redacted]

Statistical Methods:

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 part of the study. Subjects dropping out before completion will be replaced by enrolling a new subject.

Data will be listed and summarized using SAS® Version 9.2 or higher (SAS Institute, Inc., Cary, NC) according to the sponsor-agreed reporting standards, where applicable. Details of analysis methods will be documented in the statistical analysis plan.

All subjects who are exposed to zanubrutinib and/or tislelizumab will be included in the safety analysis set. All subjects for whom valid zanubrutinib and/or tislelizumab PK parameters can be estimated will be included in the PK analysis set on an as treated basis.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
AEs	adverse events
ALT	alanine aminotransaminase
anti-HBc	hepatitis B core antibody
AST	aspartate aminotransaminase
AUC	area under the plasma concentration-time curve
BCR	B-cell receptor
BID	twice a day
BTK	Bruton's tyrosine kinase
CL	clearance
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CR	complete response
CRO	contract research organization
CSF	cerebrospinal fluid
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
eCRF	electronic case report form
ECOG	Eastern Cooperative Oncology Group
ECG	electrocardiogram
EGFR	epithelial growth factor receptor
EPG	electrophoresis
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
FL	follicular lymphoma
GCB	germinal center B-cell
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCL	hairy cell leukemia
HCV	hepatitis C virus
HER	human epidermal growth factor receptor
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	50% maximal inhibiting concentration
ICU	intensive care unit
IEC	Independent Ethics Committee

IgVH	immunoglobin variable region heavy chain
IHC	immunohistochemistry
IND	investigational new drug
IRB	Institutional Review Board
IV	intravenous
LDH	lactate dehydrogenase
LVEF	left ventricular ejection fraction
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MR	minor response
MRI	magnetic resonance imaging
MTD	maximal tolerated dose
MUGA	multigated acquisition scan
MZL	marginal zone lymphoma
NCI-CTCAE	National Cancer Institute Common Toxicity Criteria
OS	overall survival
ORR	overall response rate
PCR	polymerase chain reaction
PCNSL	primary central nervous system (CNS) lymphoma
PD	progressive disease
PD-1	programmed cell death-1
PD-L1	programmed death ligand-1
PD-L2	programmed death ligand-2
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response/remission
Q2W	every 2 weeks
Q3W	every 3 weeks
QD	once a day
QTc	corrected QT wave
RP2D	recommended phase 2 dose
SAE	serious adverse event
SCNSL	secondary CNS lymphoma
SD	stable disease
SLL	small lymphocytic lymphoma
SMC	Safety Monitoring Committee
SOPs	standard operating procedures
$t_{1/2}$	terminal half-life
TEC	tyrosine kinase expressed in hepatocellular carcinoma
TIL	tumor-infiltrating lymphocyte
tislelizumab	BGB-A317
t_{max}	time to maximum observed plasma concentration
TSH	thyroid stimulating hormone
ULN	upper limit of normal

WBC	white blood cell
WHO	World Health Organization
WM	Waldenstrom macroglobulinemia
zanubrutinib	BGB-3111

1.0 INTRODUCTION

1.1 Background and Pharmacology

1.1.1 Zanubrutinib (BGB-3111)

Bruton's tyrosine kinase (BTK), a member of the tyrosine kinase expressed in hepatocellular carcinoma (TEC) family of kinases, is a critical component of the B-cell receptor (BCR) signaling cascade. Inhibition of BTK has emerged as a promising strategy for targeting B-cell malignancies. Ibrutinib has demonstrated promising anti-tumor activity in several B-cell malignancies, including mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL), follicular lymphoma (FL), multiple myeloma, and activated B-cell-like subtype of diffuse large B-cell lymphoma (DLBCL).[1,2]

Ibrutinib was approved by the US Food and Drug Administration (FDA) for treatment of MCL (November 2013) and CLL (February 2014) in subjects who had received at least 1 prior therapy.[3,4] More recently it was also approved for the treatment of subjects with CLL with 17p deletion (July 2014) and Waldenstrom macroglobulinemia ([WM]; January 2015).

While ibrutinib treatment frequently generates objective responses in these diseases, few of them are complete responses (CRs); thus management requires continuous treatment.[5,6] In addition, though ibrutinib is well-tolerated in comparison to traditional chemotherapies, it is associated with adverse reactions that in some cases can be life threatening or treatment limiting. These adverse reactions, including but not limited to skin rash, nausea, vomiting, thrombocytopenia, bleeding, and atrial fibrillation, are believed to be due to ibrutinib's off-target activities against epithelial growth factor receptor (EGFR)/Janus kinase 3/TEC.

Zanubrutinib (also known as BGB-3111) is a potent, specific, and irreversible BTK inhibitor with a favorable pharmacology/ toxicology profile. Preclinical data suggests that zanubrutinib is differentiated from ibrutinib in the following aspects:

1. Zanubrutinib is more selective than ibrutinib in the inhibition of BTK versus EGFR, Gardner-Rasheed feline sarcoma viral oncogene homolog, Fyn-related kinase, human epidermal growth factor receptor (HER)2, HER4, interleukin-2-inducible T-cell kinase, Janus kinase 3, lymphocyte-specific protein tyrosine kinase, and TEC, and therefore may have fewer off-target toxicities (eg, diarrhea).

2. Zanubrutinib has high bioavailability when administered orally and has rapid clearance in rodents and dogs. The predicted efficacious dose of zanubrutinib in subjects is much lower than ibrutinib, which also could contribute to better tolerability.

3. Due to its weaker interleukin-2-inducible T-cell kinase inhibitory activity, zanubrutinib displayed significantly less inhibitory effect on rituximab-induced antibody dependent cell-

mediated cytotoxicity than ibrutinib in preclinical studies and this could likely result in better efficacy in subjects when combined with rituximab or other antibody therapies that are dependent on antibody-dependent cell-mediated cytotoxicity.

Refer to the Investigator's Brochure (IB) for more detailed information on the background of zanubrutinib (BGB-3111).

1.1.2 Tislelizumab (BGB-A317)

The immune checkpoint-inhibitory receptor, programmed cell death-1 (PD-1), is mainly expressed in activated T-cells including CD8+ cytotoxic T-lymphocytes and CD4+ T-helper lymphocytes.[7] It is believed that PD-1 plays an important role in immune modulation of tumor progression by regulating the key inhibitory signaling in the T-cells when engaged by its ligands. The PD-1 signaling cascade negatively regulates T-cell receptor and attenuates T-cell proliferation and functional activities, leading to T-cell exhaustion. In general, PD-1 is rarely expressed on malignant B-cell-originated lymphoma cells and is frequently expressed on the T-cell lineage of tumor-infiltrating lymphocytes (TILs) in various subtypes of lymphoma, particularly those with follicular lymphoma and certain types of T-cell lymphoma. Chronic lymphocytic leukemia or small lymphocytic lymphoma is an exception because PD-1 expression is seen both on circulating malignant cells and in the tumor microenvironment. Programmed death ligand (PD-L)-1 overexpression is not usually seen in B-cell non-Hodgkin lymphoma. However, it is seen in the several disorders, including primary mediastinal B-cell lymphoma harboring a genetic mutation (9p24.1) that causes upregulation of PD-L1 and PD-L2, Epstein-Barr virus-positive lymphomas in which the virus induces PD-L1 expression, T-cell histocyte-rich diffuse large B-cell lymphoma, some cases of activated DLBCL, and lymphoplasmacytoid lymphoma.[8] Such evidence provides the basis for cancer immunotherapeutic intervention via antagonist to PD-1.

Three PD-1 inhibitors have been assessed in patients with lymphoid malignancies: pidilizumab, nivolumab, and pembrolizumab. Among them, pembrolizumab and nivolumab have been approved by FDA for treatment of advanced or unresectable melanoma. Nivolumab was approved to treat patients with advanced/metastatic squamous non–small cell lung cancer with progression on or after platinum-based chemotherapy, renal cell carcinoma as second line treatment after failure from anti-angiogenic agents, and classical Hodgkin lymphoma after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation treatment with brentuximab vedotin. Toxic effects that are life threatening are rare, and few studies report treatment-related deaths. Moreover, the anti-tumor effects of anti-PD-1 antibodies have been observed in patients with other B-cell malignancies, including DLBCL and FL. Pidilizumab was evaluated in combination with rituximab in a single-arm Phase 2 study in relapsed or refractory FL. Among 32 total patients (29 eligible), 66% of patients achieved an overall response rate, 52% showed CR, and 14% showed partial response.[9] The Phase 1 clinical study of nivolumab treated

82 patients with relapsed or refractory lymphoid malignancies. Responses were seen in 4 of 11 patients with DLBCL, 4 of 10 patients with FL, and 2 of 5 patients with peripheral T-cell lymphoma.[10] In another study, pembrolizumab was administered to 29 patients with classic Hodgkin lymphoma as a phase 1b study. These patients were extensively pretreated: 52% of them had undergone 5 or more previous lines of treatment, and all of them had received previous brentuximab therapy. Response to treatment was recorded in 20 (66%) patients, including 6 patients who showed a CR. The disease was controlled in 25 of 29 patients (86%), and the median time to drug response was 12 weeks. Toxic effects were negligible.[11]

Tislelizumab (also known as BGB-A317) is a humanized IgG4 variant monoclonal antibody against PD-1 being developed for treatment of human malignancies. Tislelizumab has demonstrated a favorable toxicology and safety pharmacology profile in nonclinical experiments. Moreover, tislelizumab binds to the extracellular domain of human PD-1 with high affinity and specificity; it potently blocks PD-1-mediated signal transduction and activates human T-cells and primary peripheral blood mononuclear cells in the *in vitro* cell-based assays, and it mobilizes immune cells inhibiting tumor growth in mouse cancer models.

1.2 Overview of Clinical Pharmacology

1.2.1 Zanubrutinib

In the Phase 1, first-in-human study of zanubrutinib as monotherapy (A Phase 1, Open-Label, Multiple-Dose, Dose Escalation, and Expansion Study to Investigate the Safety and Pharmacokinetics (PK) of the BTK Inhibitor BGB-3111 in Subjects with B-Cell Lymphoid Malignancies; protocol number BGB-3111-AU-003), interim PK data in a limited number of subjects showed that zanubrutinib is rapidly absorbed and eliminated after oral administration. The maximum serum concentration and the drug exposure (area under the concentration-time curve [AUC]) increased in a nearly dose-proportional manner from 40 mg to 320 mg, both after the single dose and at steady state. The terminal half-life ($t_{1/2}$) ranged from 1.8 hours to 3.7 hours. At 320 mg once daily (QD) and 160 mg twice daily (BID), the means for maximum observed plasma concentration (C_{max}) and the area under the concentration-time curve from 0 to 24 hours ($AUC_{0\text{-}24h}$) are around 646 ng/mL and 2,704 ng/mL*h, and 282 ng/mL and 3,006 ng/mL*h, respectively, at the steady state.

In the same Phase 1 study, the pharmacodynamics of zanubrutinib as measured by BTK occupancy in peripheral blood mononuclear cells was determined in a limited number of subjects. The data indicate that even at the starting dose (40 mg), zanubrutinib achieved rapid, durable, and near complete inhibition of BTK. These data suggest that zanubrutinib is a very potent BTK inhibitor.

Study BGB-3111-103 evaluated food effect on zanubrutinib after oral administration in human subjects. Dosing zanubrutinib with a high-fat or low-fat meal did not significantly affect the AUC of zanubrutinib. Zanubrutinib may be taken with or without food.

Results from a dedicated drug-drug interaction study (BGB-3111-104) indicated that co-administration of zanubrutinib with the strong CYP3A inducer rifampin (600 mg every day for 8 days) decreased exposure of zanubrutinib by 13.5-fold for $AUC_{0-\infty}$, and 12.6-fold for C_{max}, in healthy subjects. Co-administration of zanubrutinib with the strong CYP3A inhibitor itraconazole (200 mg every day for 4 days) increased exposure of zanubrutinib by 3.8-fold for $AUC_{0-\infty}$, and 2.6-fold for C_{max}. These results are consistent with the role for CYP3A isoenzymes as the principal metabolic pathway for zanubrutinib.

Based on the in vitro study, a clinical drug-drug interaction study (BGB-3111-108) was conducted to assess the effect of zanubrutinib on the PK of substrates of CYP3A (midazolam), CYP2C9 (warfarin), CYP2C19 (omeprazole), P-gp (digoxin), BCRP (rosuvastatin) using a cocktail approach. The results show that zanubrutinib does not significantly affect drugs metabolized by CYP2C9 (warfarin) or transported by P-gp (digoxin) and BCRP (statins). Zanubrutinib has a mild induction effect on CYP3A and CYP2C19 enzymes. AUC_{0-t} and C_{max} values were approximately 47% and 30% lower, respectively, when midazolam was coadministered with zanubrutinib. AUC_{0-t} and C_{max} values were approximately 36% and 20% lower, respectively, when omeprazole was coadministered with zanubrutinib.

1.2.2 Tislelizumab

There are 18 ongoing studies with tislelizumab, 7 with available preliminary data. For the most recent information on the clinical pharmacology experience with tislelizumab, please refer to the Investigator's Brochure. Preliminary PK analysis set showed that a 2-compartment model with first order elimination best described the PK data. Systemic clearance of tislelizumab was 0.173 L/day, volume of distribution in the central and peripheral compartment were 2.89 and 1.76 L, respectively, and terminal elimination half-life was approximately 19 days. Race, gender, and body weight are not significant covariates on the clearance of tislelizumab, which supports fixed-dosing across different ethnic groups.

1.3 Overview of Safety and Efficacy

1.3.1 Zanubrutinib

Preliminary results have demonstrated that zanubrutinib has promising anti-tumor activity in patients with B-cell malignancies, including CLL, WM, MCL, hairy cell leukemia (HCL), DLBCL, marginal zone lymphoma (MZL), and FL. As of 19 October 2015, there are 25 patients enrolled in Part 1 (dose escalation) and30 patients enrolled in Part 2 (safety, schedule, and efficacy expansion) of the study (BGB-3111-AU-003). Four doses of zanubrutinib (40 mg, 80 mg, 160 mg, and 320 mg, QD) and 2 dose regimens of zanubrutinib (320 mg QD versus 160 mg BID) had been evaluated. Twenty-five patients in Part 1 and 14 patients in Part 2 have at least 1 disease response assessment. Patients were evaluated per histology-specific standard criteria,

and the best responses were: 3 patients achieved complete CR, including 1 DLBCL patient and 2 MCL patients; 26 patients achieved partial responses/remission (PR), including 13 with CLL, 6 with WM, 6 with MCL, and 1 with HCL; 4 patients achieved stable disease (SD), including 1 patient with CLL, 1 patient with MCL, 1 patient with MZL, and 1 patient with FL. Six patients, 3 with DLBCL, 1 with WM, 1 with MCL, and 1 with Burkitt-like lymphoma, presented with progressive disease (PD).

- Complete response/remission (n = 3): 1 DLBCL patients and 2 MCL patients.
- Partial response/remission (PR; n = 26): 13 CLL patients, 6 WM patients, 6 MCL patients, 1 HCL patient.
- Stable disease (SD; n= 4): 1 CLL patients, 1 MCL patient, 1 MZL patient, 1 FL patient.
- Progressive disease (n = 6): 3 DLBCL patients; 1 WM patient, 1 MCL patient, 1 Burkitt-like lymphoma patient.

As of 19 October 2015, except for the 6 patients who had PD, all the remaining 33 patients who have had at least 1 disease assessment have received the treatment of zanubrutinib for more than 2 months. No dose limiting toxicities (DLT) were encountered, and the maximum tolerated dose (MTD) was not reached. There were no drug-related serious adverse events (SAEs). The only 4 drug-related Grade 3/4 adverse events (AEs) were neutropenia events, which were transient and did not lead to drug discontinuation. Six patients had a baseline history of atrial fibrillation/flutter, but no exacerbation or new events of atrial fibrillation/flutter were reported. For the most recent information on the clinical experience with zanubrutinib, please refer to the Investigator's Brochure.

The QT interval prolongation potential of zanubrutinib was evaluated in healthy subjects in a thorough QT study (BGB-3111-106). Results from this study demonstrated that single oral doses of zanubrutinib at a therapeutic dose of 160 mg and a supratherapeutic dose of 480 mg did not have a clinically relevant effect on ECG parameters, including QTc intervals and other ECG intervals. Because of the short half-life and no accumulation seen upon multiple-dosing, these results are also applicable for steady-state conditions.

1.3.2 Tislelizumab

As of 8 October 2015, in the ongoing Phase 1 study, 32 subjects have been enrolled in 3 escalating cohorts and 1 expansion cohort receiving tislelizumab at 0.5 mg/kg Q2W (n = 3), 2 mg/kg Q2W (n = 23), and 5 mg/kg (n = 6). Tislelizumab has been well tolerated. There were no DLTs at 0.5 mg/kg and 2 mg/kg Q2W cohorts. One DLT (Grade 3 colitis) was observed among 6 subjects treated at 5 mg/kg Q2W cohort. The dose escalation is ongoing at 10 mg/kg Q2W, and the MTD has not been reached to date. Efficacy data are too preliminary to draw conclusions. For

the most recent information on the clinical experience with tislelizumab, please refer to the Investigator's Brochure

1.4 Benefits and Risks

1.4.1 Zanubrutinib

Zanubrutinib has demonstrated a very favorable toxicology and safety pharmacology profile, as determined by pharmacologic characteristics in the ongoing clinical studies. Preliminary data show that zanubrutinib is well tolerated and has promising anti-tumor activity in advanced B-cell malignancies, including CLL, MCL, WM, HCL, DLBCL, FL, and MZL. Approximately 400 patients have been enrolled worldwide in completed and ongoing clinical trials evaluating zanubrutinib and received at least 1 dose of zanubrutinib. Available data for zanubrutinib support a positive benefit-risk profile for the use of zanubrutinib as an investigational agent for treatment of previously untreated B cell lymphoid malignancies.

Zanubrutinib is an investigational drug with only limited safety data in humans. Subjects enrolled in clinical studies with zanubrutinib must be closely monitored by means of AEs, vital signs, electrocardiograms (ECGs), and clinical laboratory safety tests of blood and urine. For further discussion on safety profile of zanubrutinib, please refer to the most recent version of the Investigator's Brochure.

1.4.2 Tislelizumab

The subjects enrolled in clinical studies with tislelizumab must be closely monitored by recording AEs, recording vital signs and ECGs, and conducting clinical laboratory safety tests of blood and urine.

Clinical experience with existing drugs of the same therapeutic class (anti-PD-1 monoclonal antibodies) suggests the most common AEs were Grade 1/2, including arthralgia, cough, diarrhea, fatigue, fever, nausea, pruritus, and rash. However, Grade 3/4 treatment-related AEs occurred in 15% of patients in the nivolumab study, and there were 3 deaths, all attributed to pulmonary toxicity.[12,13] Grade 3/4 AEs were also reported in the pembrolizumab studies, including 1 subject who died of myocardial infarction while being treated for pneumonitis/pneumonia.[14,15] Drug-related AEs of special interest (AEs with potentially immune-related etiology) included, vitiligo, pneumonitis, hepatitis, colitis, thyroiditis, and hypophysitis, which may be observed during multiple dose escalation in subjects with cancer.[16,17,18]

More than 400 patients have been treated with tislelizumab monotherapy at clinically relevant doses (≥ 2 mg/kg) and in combination. The safety profile is consistent with known class effects of anti-PD-1 antibodies, and included mostly mild/moderate AEs. Very few Grade 3/4 infusion-related AEs have been observed, which are generally reversible and manageable with study drug

interruption and/or steroid treatment. For further discussion on safety profile of tislelizumab, please refer to the most recent version of the Investigator's Brochure.

1.5 Rationale for the Combination of Zanubrutinib and Tislelizumab

As noted above, signaling via the aberrantly activated BCR pathway has a critical role in the pathogenesis of B-cell tumors by promoting survival and clonal expansion of malignant B-cells. Ibrutinib, a FDA-approved BTK inhibitor, has demonstrated objective responses among different B-cell malignancies in clinical studies, including CLL/small lymphocytic lymphoma (SLL), MCL, DLBCL, FL, and WM. Zanubrutinib is a more potent, more specific second-generation BTK inhibitor than ibrutinib. In the ongoing Phase 1 study (BGB-3111-AU-003), zanubrutinib has been shown to be well tolerated, safe, and active in various histopathological subtypes of B-cell malignancies.

Early clinical studies using PD-1 inhibitors have also shown significant clinical activity in various subtypes of relapsed lymphoma and a superior safety profile. PD-1 inhibitors are moving into later phases of clinical studies in hematologic malignancies and are being evaluated in the treatment of refractory/relapsed lymphomas (non-Hodgkin lymphoma and Hodgkin lymphoma) and will likely be used for earlier-line treatment of B-cell malignancies. The combination of PD-1/PD-L1 inhibitors (i.e., nivolumab, pembrolizumab, and MEDI-4736) with BCR pathway inhibitors (i.e., ibrutinib and ACP-196), are being evaluated in different B-cell malignancies with the expectation of greater benefit for patients.

This study is designed to evaluate the safety, tolerability, and PK profile, as well as preliminary anti-tumor activity of zanubrutinib, in combination with tislelizumab in subjects with B-cell malignancies. The doses and regimens of zanubrutinib and tislelizumab are selected based on the PK, safety and tolerability, pharmacodynamics, and preliminary efficacy in the ongoing zanubrutinib study (BGB-3111-AU-003) and tislelizumab study (BGB-A317_Study_001).

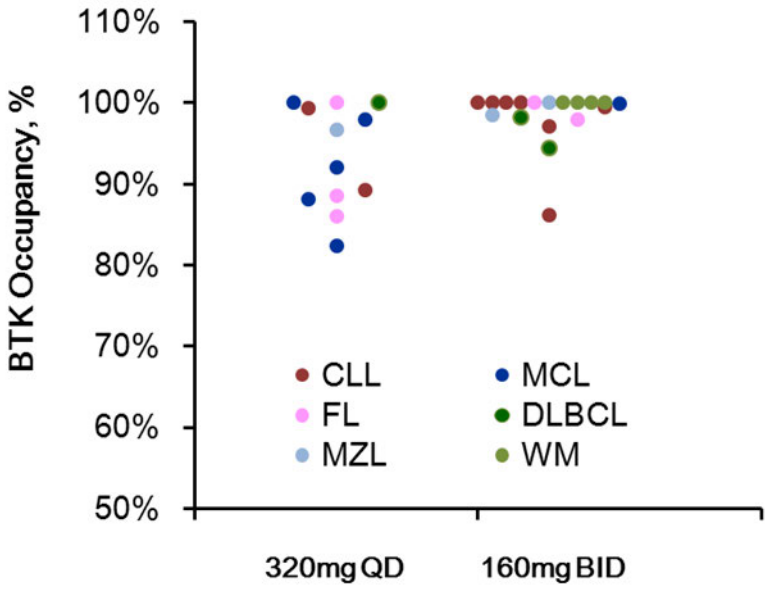
The study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) guidelines, the Declaration of Helsinki, and any applicable regulatory requirements.

1.6 Rationale for Zanubrutinib Dose and Schedule

In the ongoing Phase 1 study of zanubrutinib monotherapy in patients with B-cell malignancies, 30 subjects from the study receiving either zanubrutinib 320 mg orally QD (n = 12) or 160 mg orally BID (n = 18) were evaluated for BTK occupancy in lymph node tissue using a fluorescent probe assay on paired lymph node biopsies. Median occupancy was 100% in patients receiving zanubrutinib 160 mg BID (n = 18) versus 94% in patients receiving zanubrutinib 320 mg QD (n = 12; p = 0.002, Wilcoxon test). The proportion of subjects with ≥ 90% BTK occupancy was 94% (160 mg BID) versus 58% (320 mg QD; p = 0.027, Fisher's Exact test). Occupancy did not

appear to differ among histologic subtypes. The BTK occupancy in lymph node tissue by dose/schedule is shown in Figure 1-1.

Figure 1-1. Bruton's Tyrosine Kinase Occupancy in Lymph Node Tissue from Patients with Different Types of Lymphoma and Doses of Zanubrutinib



BTK = Bruton's tyrosine kinase; CLL = chronic lymphocytic leukemia; FL = follicular lymphoma; MZL = marginal zone lymphoma; MCL = mantle cell lymphoma; DLBCL = diffuse large B-cell lymphoma; WM = Waldenstrom macroglobulinemia; QD = once a day; BID = twice a day.

The effect of food on zanubrutinib exposure has also been evaluated in a dedicated food-effect study in healthy volunteers (Study BGB-3111-103). Co-administration of zanubrutinib with low-fat or high-fat food did not result in any clinically meaningful changes in C_{max} or AUC. Subjects will be allowed to take zanubrutinib with or without food.

1.7 Rationale for Tislelizumab Flat Dose and Schedule

The fixed dose of tislelizumab at 200 mg for dose escalation level 3 and Cohort 4A of the dose expansion was selected on the basis of both nonclinical studies and available clinical data as described below.

No tissue cross-reactivity was found in either human or monkey tissues, nor was any effect on cytokine release observed in human whole-blood assays. No apparent toxicity was noted in either mice or monkeys following a single dose up to 100 mg/kg or in monkeys following a repeat dose up to 30 mg/kg biweekly for 13 weeks. The toxicokinetics profile was characterized in monkey

studies, and the systemic exposure appeared to be dose proportional without sex differences or accumulation over the dosing period. No apparent immunotoxicity was observed, as no apparent changes in clinical pathology or histopathology were noted in these studies.

The tislelizumab dose is also informed by available clinical activity, safety, and PK data. The safety of tislelizumab has been tested across a range of doses in Study BGB-A317-001 (0.5 mg/kg to 10 mg/kg Q2W [n = 62]; 2 mg/kg to 5 mg/kg Q3W [n = 41]) with no MTD defined at the highest dose examined. MTD is the highest dose at which < 33% of the subjects experience a DLT, which may not be reached in the 4 planned doses. The recommended Phase 2 dose (RP2D) will be the dose at or below MTD identified in the dose escalation part of the study. It will be determined by taking safety, efficacy, and PK into consideration.) Based on recommendation of the Safety Monitoring Committee, tislelizumab at 5 mg/kg Q3W was selected as the dose for the indication expansion part of Study BGB-A317-001 (Phase 1B). Efficacy was demonstrated in 15 of 99 evaluable subjects to date who had been diagnosed with a variety of tumor types and were treated with single agent tislelizumab at doses that ranged from 2 mg/kg to 5 mg/kg administered either Q2W or Q3W. According to the Phase 1A PK data from Australia, plasma concentrations of tislelizumab showed linear relationships for doses ranging from 0.5 mg/kg Q2W to 10 mg/kg Q2W. Furthermore, according to the results of analysis of covariance, there was no significant correspondence between the weight of subjects and the in vivo clearance rate of tislelizumab. This conclusion supports fixed-dose administration. Simulations also do not suggest any clinically meaningful differences in exposure following fixed dose or dose adjusted for weight. [19] On the basis of these analyses, a fixed dose of 200 mg was selected (equivalent to a weight-based dose of 3.3 mg/kg, calculated with 60 kg) for Dose Level 3 and Cohort 4A.

Selection of a Q3W dosing interval is supported by this preliminary PK evaluation, which will also allow convenient potential integration with common chemotherapeutic regimens.

All available PK, safety, and efficacy data for tislelizumab will continue to be evaluated as described above to support the proposed 200-mg fixed dose.

2.0 STUDY OBJECTIVES

2.1 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.

2.2 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.

2.3 Exploratory Objectives

- [redacted]

3.0 STUDY ENDPOINTS

3.1 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).

3.2 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.

3.3 Exploratory Endpoints

- [redacted]

4.0 INVESTIGATIONAL PLAN

4.1 Summary of Study Design

This 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, 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. Refer to Section 5.2 for further dosage and administration details.

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 will be immediately activated with Amendment 5.0.

4.1.1 Dose-Limiting Toxicity

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

Subjects who received < 80% of the tislelizumab infusion in Cycle 1 (eg, the infusion had to be discontinued due to an infusion reaction) and did not experience a DLT will not be taken into account in the assessment of the overall DLT rate for the particular dose level cohort and will need to be replaced in the dose-escalation cohort.

Subjects who did not complete the first cycle of zanubrutinib (28 days) and did not experience a DLT will not be taken into account in the assessment of the overall DLT rate for the particular dose level cohort and will need to be replaced in the dose-escalation cohort.

Resumption of zanubrutinib and tislelizumab administration for subjects experiencing DLTs may be permitted, according to the criteria described in Section 4.1.2, if clinically appropriate, contingent on the return of the DLT to baseline or ≤ Grade 1 severity and interruption or delay of treatment for no more than 6 weeks from scheduled dose.

4.1.2 Drug Hold and Dose Modification

The continuous safety evaluation will be performed by the sponsor, the coordinating investigator, and investigators. The Safety Monitoring Committee ([SMC]; refer to Section 7.3.1 for composition and responsibility) will be established for the determination of dose levels to be administered during the study.

Where possible, the investigator should determine which of the 2 investigational agents is responsible for the toxicity; in the case where the investigator is unable to assign causality to 1 specific agent, both drugs must be held. Dosing will be held for individual subjects under any of the following conditions (assuming that the condition is assessed as related to study drug and not the underlying disease):

- Grade 4 neutropenia (lasting > 7 days) not attributable to active leukemia or lymphoma
- Grade ≥ 3 febrile neutropenia
- Grade 4 thrombocytopenia (lasting > 7 days) not attributable to active leukemia or lymphoma
- Grade 3 thromobocytopenia associated with bleeding
- For patients with baseline platelet count ≥ 35 x 10^9/L but < 50 x 10^9/L, platelet count < 35 x 10^9/L associated with bleeding
- Grade 2 or higher immune-related events (See Section 9.14.1.2 and Section 9.14.2.4 for more specific instructions)
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 and up to 5 times upper limit of normal (ULN) or total bilirubin > 1.5 and up to 3 times ULN. For subjects with liver infiltration by disease who entered the study with Grade 2 elevation of AST/ALT, tislelizumab will be withheld if AST/ALT increase is ≥ 50% relative to baseline
- Any Grade ≥ 3 nonhematologic toxicities suspected to be related to study drug treatment and not covered above, with the following exceptions:
  - laboratory abnormalities deemed nonserious by the investigator
  - Grade 3 tumor flare
  - infusion reaction that has resolved to ≤ Grade 1 within 28 days
  - atrial fibrillation or hypertension adequately controlled with oral medication

After complete resolution or improvement of the toxicity to Grade 1 or to baseline values within 21 days, the investigator may elect to have the subject restart the treatment. If the subject's toxicity improves to Grade 1 or baseline within 22 to 42 days of study drug discontinuation, and if, in the investigator's opinion, it is in the subject's best interest to restart treatment, then a written approval must be obtained from the sponsor medical monitor.

If zanubrutinib is held, and in the investigator's opinion, the toxicity is unrelated to zanubrutinib, the subject may be restarted at the dose preceding the event. However, if the toxicity recurs, the dose must be reduced to 50% of preceding dose. If, in the investigator's opinion, the toxicity is related to zanubrutinib, the subject may restart therapy at 50% of preceding dose. For example, if a subject started with 160 mg BID, 50% dose reduction would be 80 mg BID. A second dose reduction to 80 mg QD, based on the criteria outlined above, may be considered upon consultation with the sponsor medical monitor. Any subjects who do not tolerate 80 mg QD must be removed from the study. Following dose reduction and resolution of the event, rechallenge to the dose prior to reduction may be possible with approval from the medical monitor.

The administration of tislelizumab will be resumed at the same dose according to the original schedule. See Section 9.14.2.4 for more specific instructions related to tislelizumab.

If, in the investigator's opinion, the toxicity is related to 1 of the study drugs and the drug is discontinued, the subject may be continuously treated with the other study drug if the subject is benefiting from the treatment in the judgment of the investigator.

Detailed guidelines for specific AEs related to tislelizumab are given in Section 9.14.2.4. Permanent discontinuation criteria for both zanubrutinib and tislelizumab are outlined in Section 4.2.4.3.

4.1.3 Schedule of Assessments

The Schedules of Assessments are presented in Table 4-1 and Table 4-2. PK and anti-drug antibody (ADA) sampling are presented in Table 4-3 and Table 4-4.

Table 4-1 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		
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		

	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**
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 antibodies[24]				X			X	X		
Archival tumor tissues[25]	X									
Fresh tumor tissues[25]	X			X				X		
PK blood sampling[26]		X	X				X			
Pulmonary function tests[27]	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**
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 < 1.0×10^9/L) or thrombocytopenia (platelets count < 50×10^9/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. For the rest of subjects, upon consent (optional), an archival tumor tissue or a fresh tumor biopsy if feasible, will be collected at screening for biomarker analysis. 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 4-2 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]	

	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**
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 tap[23]	X	End of Cycles 2, 4, 6, 8, 10, 12, 14, and 16			X		
CSF 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 < 1.0×10^9/L) or thrombocytopenia (platelets count < 50×10^9/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] Upon consent (optional), an archival tumor tissue or a fresh tumor biopsy if feasible, will be collected at screening for biomarker analysis. 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.

[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.)

Table 4-3 Pharmacokinetic/ADA Sampling and Safety Measurements From the First 30 Subjects (Dose Escalation)

Procedure	Cycle 1 Day 1					Cycle 1 Day 2	Cycle 1 Day 8	Cycle 2 Day 1					Cycle 3 Day 1		Cycle 4 Day 1		Cycles 6, 8, 12, and 16 Day 1	Safety Follow-up
Hours	**Predose**	**1**	**2**	**4**	**7**	**Predose**		**Predose**	**1**	**2**	**4**	**7**	**Predose**	**4**	**Predose**	**4**		
PK blood sampling for Zaubrutinib	X[1]	X[2]	X[3]	X[3]	X[4]	X[1]		X[1]	X[2]	X[2]	X[2]	X[4]						
PK blood sampling for tislelizumab							X[1]	X[1]			X[3]		X[1]	X[3]	X[1]	X[3]	X[1]	X
ADA blood sampling for tislelizumab							X[1]	X[1]							X[1]		X	X
Vital signs and ECGs(in triplicate)	X		X					X			X		X	X	X	X		

ADA = anti-drug antibody; ECG = electrocardiogram; PK = pharmacokinetics.
General note: When the two study drugs are administered on the same day (except on the days both PK samples to be collected), zanubrutinib should be taken at least 30 minutes before tislelizumab infusion. Except for predose PK, each PK sampling time point of tislelizumab and zanubrutinib will be in correspondence with the end of dosing of each agent, respectively. For tislelizumab, the time point relates to the end of the infusion. It is important that PK sampling occur as close as possible to the scheduled time. To achieve this, some other assessments scheduled at the same time need to be initiated prior to or after the time point to allow for these measurements to be completed with sufficient time for PK sampling at the designated time point. Thus, the sequence at a particular time point is: 1) scheduled ECG; 2) vital sign measurements; 3) PK blood samples (to be performed at the precise protocol scheduled time); and 4) any other scheduled or unscheduled measurements at that time point.
[1] Within 2 hours prior to dosing.
[2] Window of ±10 minutes.
[3] Window of ±20 minutes.
[4] Window of ±1 hour.

Table 4-4 Pharmacokinetic/ADA Sampling and Safety Measurements (Dose Expansion)

Expansion Cohort												
Procedure	**Cycle 1 Day 1**			**Cycle 2 Day 1**	**Cycles 2, 6, 12 Day 21 (optional)[5]**		**Cycle 5 Day 1**			**Cycle 9 Day 1**	**Cycle 17 Day 1**	**Safety Follow Up**
Hours	**Predose**	**2 hours**	**Within 30 min after the end of infusion**	**Predose**	**Predose**	**2 hours**	**Predose**	**2 hours**	**Within 30 min after the end of infusion**	**Predose**	**Predose**	
PK for Zanubrutinib	X[1]	X[2]			X[1]	X[2]	X[1]	X[2]				
PK for tislelizumab	X[1]		X[3]	X[1]	X[1]	X[2]	X[1]		X[3]	X[1]	X[1]	X
ADA for tislelizumab	X[1]			X[1]			X[1]			X[1]	X[1]	X
Vital signs and ECGs (in triplicate)[4]	X	X					X	X				

ADA = anti-drug antibody; ECG = electrocardiogram; PK = pharmacokinetics.
General note: When the 2 study drugs are administered on the same day (except on the days both PK samples to be collected), zanubrutinib should be taken at least 30 minutes before tislelizumab infusion. Except for predose PK, each PK sampling time point of tislelizumab and BGB-290 will be in correspondence with the end of dosing of each agent, respectively. For tislelizumab, the time point relates to the end of the infusion. It is important that PK sampling occur as close as possible to the scheduled time. To achieve this, some other assessments scheduled at the same time need to be initiated prior to or after the time point to allow for these measurements to be completed with sufficient time for PK sampling at the designated time point. Thus, the sequence at a particular time point is: 1) scheduled ECG; 2) vital sign measurements; 3) PK blood samples (to be performed at the precise protocol scheduled time); and 4) any other scheduled or unscheduled measurements at that time point.
[1] Within 2 hours prior to dosing.
[2] Window of ±20 minutes.
[3] Within 30 minutes after the end of infusion of tislelizumab.
[4] In the first 30 subjects only.
[5] If subjects have CSF collected for disease assessment, 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 drug measurement is optional.

4.2 Selection of Study Population

Approximately 85 subjects will be required to complete the Phase 1b study of zanubrutinib in combination with tislelizumab.

4.2.1 Inclusion Criteria

Subjects may be entered in the study only if they meet all of the following criteria:

1. Dose escalation for Dose Levels 1, 2, and 3: Subjects with relapsed or refractory World Health Organization (WHO) classification-defined B-lymphoid malignancy following at least 1 line of therapy, with no therapy of higher priority available, including CLL/SLL, MCL, FL, HCL, MZL, non-germinal center B-cell (GCB) DLBCL, GCB DLBCL, transformed FL, and Richter's transformation (NOTE: subjects with WM are excluded from enrollment as of Amendment 3).

2. Dose expansion for Cohorts 1 to 4: Subjects with either of the following relapsed or refractory WHO-classified lymphoid malignancies who have received at least 1 prior line of standard therapy:

    a. Cohort 1: GCB DLBCL, with cell of origin defined by either immunohistochemistry or gene expression profiling.
    b. Cohort 2: non-GCB DLBCL, with cell of origin defined by either immunohistochemistry or gene expression profiling. Subjects who have transformed to DLBCL from another histology may be enrolled into Cohort 3.
    c. Cohort 3: Transformed lymphoid malignancy, including but not limited to:
        i. Large cell transformation of chronic lymphocytic leukemia (Richter's transformation).
        ii. Large cell transformation of other WHO-classified indolent non-Hodgkin's lymphoma, including FL, or MZL.
    d. Cohort 4: Histologically confirmed PCNSL or SCNSL of breast or testicular origin:
        i. Must be able to tolerate lumbar puncture and/or Ommaya taps.
        ii. Must have received at least 1 prior central nervous system (CNS)-directed therapy.
        iii. Presence of brain parenchymal and/or leptomeningeal disease.

3. Aged ≥ 18 years, able and willing to provide written informed consent and to comply with the study protocol.

4. Measurable disease for non-Hodgkin lymphoma defined as ≥ 1 nodal lesion that is > 15 mm in the longest diameter and can be accurately measured in at least 2 dimensions with computed tomography (CT) scan, or ≥ 1 extra-nodal lesion that is > 10 mm in the longest

diameter and can be accurately measured in at least 2 dimensions with CT scan, except for PCNSL or SCNSL.

5. Subjects with an accessible tumor lesion must agree to a tumor biopsy at screening and another before the drug administration on Cycle 1 Day 8, ideally taken from the same tumor lesion, for biomarker analysis (up to first 12 qualified subjects), except for PCNSL. Additionally, subjects with DLBCL must have archival tumor tissue or agree to a tumor biopsy for confirmation of the DLBCL subtype.
6. Laboratory parameters as specified below:

    a. Hematologic: Platelet count $\geq 50 \times 10^9$/L; absolute neutrophil count $\geq 1.0 \times 10^9$ cells/L; subjects with neutrophils $< 1.0 \times 10^9$/L unless cytopenias are a direct result of active leukemia or lymphoma, in which case platelet count $\geq 35 \times 10^9$/L, absolute neutrophil count $\geq 0.75 \times 10^9$/L are allowed. (Note: Platelet transfusion administered ≤ 7 days of screening to raise pre-treatment platelet count to ≥ 35 x 10^9/L is prohibited.)

    b. Hepatic: Total bilirubin ≤ 1.5 the ULN or $\leq 2.0 \times$ ULN for subjects with Gilbert syndrome, AST, and ALT $\leq 3 \times$ ULN.

    c. Renal: Creatinine clearance ≥ 30 mL/min (as estimated by the Cockcroft-Gault equation or as measured by nuclear medicine scan or 24-hour urine collection). Subjects requiring hemodialysis will be excluded.

7. Anticipated survival of at least 4 months.
8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
9. Female subjects of childbearing potential and nonsterile males must practice at least 1 of the following methods of birth control with partner(s) throughout the study and for ≥ 3 months after discontinuing study drug: total abstinence from sexual intercourse, double-barrier contraception, intrauterine device or hormonal contraceptive initiated at least 3 months prior to first dose of study drug.
10. Male subjects must not donate sperm from initial study drug administration until 180 days after drug discontinuation.

4.2.2 Exclusion Criteria

Subjects will not be entered in the study for any of the following reasons:

1. Known, active, CNS lymphoma or leukemia, except for Cohorts 4.
2. Diagnosis with Waldenstrom's macroglobulinemia (WM).

3. For PCNSL and SCNSL (Cohorts 4):
    a. Require corticosteroid therapy > 16 mg dexamethasone daily or equivalent.
    b. Corticosteroid therapy ≤ 16 mg dexamethasone daily or equivalent at study entry from which, in the Investigator's opinion, it is expected that the subject cannot be tapered off after the first 4 weeks of study treatment.
    c. Intraocular PCNSL without evidence of brain disease.
    d. SCNSL actively receiving treatment for extra-CNS disease.
    e. PCNSL actively receiving concomitant local or systemic therapy for CNS disease.
4. Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenia purpura.
5. History of stroke or cerebral hemorrhage within 6 months of enrollment.
6. History of significant cardiovascular disease, defined as:
    a. Congestive heart failure greater than New York Heart Association (NYHA) class II according to the NYHA functional classification.
    b. Unstable angina or myocardial infarction with 6 months of enrollment.
    c. Serious cardiac arrhythmia or clinically significant ECG abnormality: corrected QT wave (QTcF) > 480 msec based on the Fridericia's formula or other ECG abnormalities including second-degree atrioventricular block type II, third-degree atrioventricular block. Subjects who have a pacemaker will be allowed on study despite ECG abnormalities or the inability to calculate the QTc.
7. Severe or debilitating pulmonary disease (dyspnea at rest, significant shortness of breath, congestive obstructive pulmonary disease).
8. History of severe allergic or anaphylactic reactions to monoclonal antibody therapy.
9. Prior BTK inhibitor or anti-PD-1/anti-PD-L1 treatment.
10. Any illness or condition that in the opinion of the investigator may affect safety of treatment or evaluation of any study endpoint.
11. Active autoimmune diseases or history of severe autoimmune diseases ; these include but are not limited to a history of immune related neurologic disease, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barre syndrome, myasthenia gravis,

systemic lupus erythematosus, rheumatoid arthritis, connective tissue diseases, scleroderma, inflammatory bowel disease, Crohn's disease, ulcerative colitis, autoimmune hepatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, or clinically manifest antiphospholipid syndrome. Note: Subjects are permitted to enroll if they have vitiligo, eczema, type I diabetes mellitus, or endocrine deficiencies, including thyroiditis managed with replacement hormones including physiologic doses of corticosteroids. Subjects with Sjögren's syndrome and psoriasis controlled with topical medication and subjects with positive serology, such as antinuclear antibodies or antithyroid antibodies should be evaluated for the presence of target organ involvement and potential need for systemic treatment but should otherwise be eligible.

12. A condition requiring systemic treatment with either corticosteroids (> 20 mg daily prednisone or equivalent) or other immunosuppressive medications within 14 days of study drug administration, except for PCNSL and SCNSL. Note: adrenal replacement doses ≤ 20 mg daily prednisone or equivalents are permitted in the absence of active autoimmune disease; subjects are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption).

13. History of interstitial lung disease or noninfectious pneumonitis, except for those induced by radiation therapy.

14. Requirement for medications which strong cytochrome P450 (CYP)3A inhibitors or inducers.

15. Vaccination with a live vaccine within 28 days of the initiation of treatment.

16. A candidate for hematopoietic stem cell transplantation or have received prior autologous hematopoietic stem cell transplant within the past 6 months. Subjects are excluded if they had received prior allogeneic stem cell transplantation.

17. Participated in any investigational drug study within 28 days or not recovered from toxicity of any prior chemotherapy to Grade ≤ 1.

18. History of other active malignancies within 2 years of study entry, with the exception of adequately treated in-situ carcinoma of cervix; localized basal cell or squamous cell carcinoma of skin; or previous malignancy confined and treated locally (surgery or other modality) with curative intent.

19. Major surgery in the past 4 weeks prior to the first day of screening.

20. Active and symptomatic fungal, bacterial, and/or viral infection; human T-cell lymphotropic virus type 1 seropositive status.

21. Human immunodeficiency virus (HIV) infection, or active hepatitis B (eg, hepatitis B surface antigen [HBsAg] reactive) or hepatitis C (eg, hepatitis C virus [HCV] ribonucleic acid [RNA] detected.
    - Hepatitis B/C serologic markers and viral load will be tested at screening. The hepatitis B testing includes HBsAg, HBcAb, and HBsAb as well as hepatitis B virus (HBV) DNA by PCR if the subject is negative for HBsAg but HBcAb positive (regardless of HBsAb status). The hepatitis C testing includes Hepatitis C virus (HCV) antibody as well as HCV RNA by PCR if the subject is HCV antibody positive. Subjects with positive HBsAg and/or detectable level of HBV DNA or detectable level of HCV RNA (≥ 15 IU/mL) are not eligible. Subjects negative for HBsAg, HBcAb positive, and HBV DNA negative must undergo monthly HBV DNA screening by PCR. Subjects positive for HCV antibody but negative for HCV RNA (defined as < 15 IU) must undergo monthly HCV RNA screening.

22. Inability to comply with study procedures.

23. Pregnant or nursing women.

24. Men or women of childbearing potential who refuse to use an adequate measure of contraception, unless they have past medical history of surgical sterilization.

25. Currently taking or plan to take CNS penetrant therapy such as thiotepa, cytarabine, or partially CNS penetrant agents known to be active in lymphoid tumors, such as rituximab.

26. Has taken or plans to take any chemotherapy, immunotherapy (eg, interleukin, interferon, thymoxin), or any investigational therapies to treat leukemia or lymphoma within 28 days or 5 half-lives (whichever is shorter) of the first study drug administration, including CNS penetrating agents. Has received radiotherapy to treat leukemia or lymphoma within 21 days of the first study drug administration.

4.2.3 Other Eligibility Criteria Considerations

To assess any potential impact on subject eligibility with regard to safety, the investigator must refer to the IB for zanubrutinib and the IB for tislelizumab for detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the investigational product being used in this study.

4.2.4 Subject Completion and Withdrawal

4.2.4.1 Subject Completion

Study treatment duration is not limited and continues until one of the events listed in Section 4.2.4.3 occurs. Since there is no maximum treatment duration, a subject will be considered complete if he/she has completed at least 1 full cycle of zanubrutinib plus tislelizumab treatment and has not withdrawn from the study prior to completing the first cycle. A subject who discontinues due to a DLT before completing the first cycle will be considered complete as well. Incomplete subjects may result in additional enrollment, as needed (i.e. to meet minimum number of DLT-evaluable subjects in dose-escalation cohorts).

If a subject discontinues from the study, the procedures will be followed as described in Section 4.2.4.2.

Subjects continuing to show clinical benefit at study closure will be allowed to participate in the long-term extension study at the discretion of the sponsor/investigator.

4.2.4.2 Subject Withdrawal/Discontinuation

Subjects may withdraw at any time or be dropped from the study at the discretion of the investigator should any untoward effects occur. In addition, a subject may be withdrawn by the investigator or the sponsor if he/she violates the study plan or for administrative and/or other safety reasons. When a subject discontinues/withdraws prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. Any adverse experiences which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 9.0.

In the event that a subject is prematurely discontinued from the study at any time due to an AE (as defined in Section 9.1), the procedures stated in Section 9.0 must be followed.

Subjects that are part of dose escalation cohorts who drop out or are withdrawn for any reason that does not fall under DLT will be considered for replacement in the cohort after due consideration from the sponsor and safety committee.

Discontinuing one or both study drugs does not require the subject to discontinue the study: subjects should still continue with study procedures, either on study drug or in follow-up, as appropriate (see Section 4.1.3).

4.2.4.3 Subject Withdrawal from the Investigational Product

Treatment with *both* zanubrutinib and tislelizumab will permanently discontinue when one of the following events occurs:

- Confirmed disease progression (refer to Section 7.7)
- Need for prohibited medication
- Subject withdrawal of consent
- Subject is lost to follow-up
- Pregnancy in subject
- Lack of compliance with the study and/or study procedures (eg, administration instructions, study visits)
- Study closure

Treatment with *either* zanubrutinib or tislelizumab (per drug, as applicable) will permanently discontinue when one of the following events occurs:

- Unresolved toxicity leading to a treatment delay of more than 21 days (unless Investigator and Sponsor Medical Monitor approval was obtained)
- Treatment delay of more than 42 days for reasons unrelated to unresolved toxicity (with the exception of subjects whose delays are related to prophylactic vaccinations or to specific consultation and agreement between the investigator and the sponsor Medical Monitor, in settings where benefit/risk may justify continued study therapy)
- Unacceptable adverse experiences (see Section 9.0)
- Intercurrent illness that prevents further administration of treatment
- If, in the opinion of the investigator, a change or discontinuation of therapy would be in the best interest of the subject
- Discontinuation of study drug by the sponsor

Treatment with zanubrutinib will permanently discontinue if one of the following occurs:

- Adverse events as indicated in Section 9.14.1.
- Subject cannot tolerate 80 mg QD.

Treatment with tislelizumab will permanently discontinue if any adverse events indicated in Section 9.14.2 occur.

In the event that a subject is prematurely discontinued from study drug at any time due to an AE (as defined in Section 9.1), the procedures stated in Section 9.0 must be followed. The

investigator or study coordinator must notify the sponsor immediately when a subject has been discontinued / withdrawn due to an adverse experience.

Subjects who discontinue study drug due to reasons other than disease progression will remain on study and should be follow the guidance provided in Section 7.4.

5.0 STUDY TREATMENTS

5.1 Description of Investigational Product

Subjects will receive zanubrutinib orally as 80-mg white, opaque capsules.

Subjects will receive tislelizumab by intravenous (IV) infusion using a single-use vial (20R glass, USP Type I) containing a total of 100 mg antibody in 10-mL isotonic solution.

5.2 Dosage and Administration

Zanubrutinib will be administered orally every 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) 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) as described below.

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. For Amendment 5.0, Cohort 4A is being discontinued. There were no safety or tolerability signals that led to the discontinuation of Cohort 4A. Cohort 4B will be immediately activated with Amendment 5.0. As of March 2019, 3 subjects with CNSL have been enrolled in Cohort 4A; however, no subjects remain on study treatment in this cohort, which is now closed to treatment and further enrollment. For Cohort 4B, 10 subjects with PCNSL and SCNSL will receive combination zanubrutinib and tislelizumab at the RP2D defined by the dose escalation starting at Day 1 of Cycle 1 and all cycles thereafter. 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. All cycles will be 21 days.

Subjects will continue to take zanubrutinib and tislelizumab as scheduled until one of the events listed in Section 4.2.4.3 occurs.

5.2.1 Zanubrutinib

Zanubrutinib will be administered orally every day (320 mg QD or 160 mg BID) with or without food. 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. Subjects will be advised that if a dose of zanubrutinib is not taken at the scheduled time, they should take the missed dose as soon as they remember and return to the normal schedule for the next dose. Subjects should skip the missed dose if it is 4 hours or less to the next scheduled dose. An extra dose of zanubrutinib should not be taken to make up for the missed dose.

Subjects will continue to take zanubrutinib until one of the events listed in Section 4.2.4.3 occurs. Subjects may discontinue tislelizumab for toxicity and continue on a single-agent of zanubrutinib .

5.2.2 Tislelizumab

Tislelizumab will be administered intravenously (2.0 mg/kg, 5.0 mg/kg, or 200 mg flat dose, depending on assigned dose level cohort) Q3W, using a volumetric pump through an IV line containing a sterile, nonpyrogenic, low-protein binding 0.2 micron in-line or add-on filter. Specific instructions for product preparation and administration are provided below; refer to Pharmacy Manual for additional details.

There will be no dose adjustments allowed for tislelizumab. In the case that an infusion cannot be administered at a scheduled visit, it is to be administered as soon as possible. If there is a dosing delay of between 1 and 10 days, the procedures at the original scheduled visit should be performed. If the delay is more than 10 days, the tislelizumab study drug infusion should be held and administered on Day 1 of the next planned cycle. The infusion at the original scheduled visit will be considered a missed dose. Subjects with infusion delays > 42 days should discontinue treatment (with some exceptions, see Section 4.2.4.3).

Guidelines for dose modification, treatment interruption, or discontinuation and for the management of immune-related AEs are provided in detail in Section 9.14.2.4.

Subjects will continue to take tislelizumab until one of the events listed in Section 4.2.4.3 occurs. Should subjects discontinue zanubrutinib for toxicity, tislelizumab monotherapy may be continued.

As a routine precaution, subjects who were enrolled in this study must be observed for 2 hours after the initial infusion, in an area with resuscitation equipment and emergency agents.

Refer to the Pharmacy Manual for detailed instructions on drug preparation, storage, and administration. For management of toxicity, refer to Section 9.14.2.

5.2.3 Dose Escalation

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

- Dose level 1: zanubrutinib 320 mg once a day (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 DLTs observed. DLTs are defined in Section 4.1.1. 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.
- ≥ 33% of subjects (eg, 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 subjects, 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 SMC (Section 7.3.1).

5.2.4 Dose Escalation for Safety Expansion (Additional Subject Enrollment for Dose Levels 1, 2, and 3)

Once a dose level has been determined not to have exceeded the MTD, up to 9 additional subjects may be enrolled to that dose level cohort (eg, 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 of the study. More than 9 additional subjects may be enrolled if requested by the SMC for additional safety information (see Section 7.3.1). If dose level 3 has cleared, these subjects will be converted to dose level 3 dosing.

5.2.5 Dose Expansion

In the dose expansion, there will be 4 dose expansion cohorts at the RP2D for the combination of tislelizumab and zanubrutinib (see Section 4.2.1 for the specific inclusion requirements of each cohort):

- Cohort 1 (n = 10): GCB DLBCL
- Cohort 2 (n = 10): non-GCB DLBCL
- Cohort 3 (n = 20): Transformed lymphoid malignancy
- Cohort 4: Primary CNS lymphoma 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.

5.3 Treatment Assignment

Each study subject will be identified by a unique subject number, which will be assigned after the subject signs the informed consent. Each subject receiving zanubrutinib and/or tislelizumab will also receive a treatment allocation number. Subject and treatment numbers will be assigned in chronological order, starting with the lowest number. Once a subject number and treatment number have been assigned to a subject, it cannot be reassigned to any other subject.

If a subject needs to be replaced in a cohort, a new subject will be enrolled for this purpose.

5.4 Packaging and Labeling

The capsule of zanubrutinib will be provided in a child-resistant closure and be labeled with space to enter the subject number and name of investigator. Tislelizumab will be provided in aseptic glass vials with a Flurotec-coated butyl rubber stopper and an aluminum cap packaged in cartons.

The primary labels on the zanubrutinib and tislelizumab packaging will be in accordance with all applicable local regulatory requirements.

5.5 Handling and Storage

The investigational products will be dispatched to a study center only after receipt of the required documents in accordance with applicable regulatory requirements and the sponsor's procedures.

Investigational product must be dispensed or administered according to procedures described herein. Only subjects enrolled in the study may receive investigational product, in accordance with all applicable regulatory requirements. Only authorized study center personnel may supply or administer investigational product. All investigational products must be stored in a secure area with access limited to the investigator and authorized study center personnel and under physical conditions that are consistent with investigational product-specific requirements.

Zanubrutinib must be kept at the condition as specified on the labels or according to the latest version of the IBs.

Tislelizumab does not contain a preservative. Unreconstituted vials should be stored at a temperature between 2°C to 8°C (36°F to 46°F) and protected from light. Refer to the Pharmacy Manual for details regarding IV administration, accountability, and disposal. Please also refer to the Investigator's Brochure for other details regarding tislelizumab.

5.6 Product Accountability

The investigator is responsible for investigational product accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the investigator or designated study center personnel must maintain investigational product accountability records throughout the course of the study. This person will document the amount of investigational products received from the sponsor and the amount supplied and/or administered to and returned by subjects, if applicable.

After completion of the study, all unused zanubrutinib and tislelizumab will be inventoried and packaged for return shipment by the hospital unit pharmacist. The inventoried supplies will be returned to the sponsor or destroyed on site, after receiving written sponsor approval.

5.7 Assessment of Compliance

On all visits to the study center, subjects will be questioned in regard to compliance with study instructions.

5.8 Treatment of Investigational Product Overdose

Overdose is defined as the subject having taken (accidentally or intentionally) a dose exceeding the dose prescribed in the protocol by 20%. Subjects with a suspected overdose should be managed with appropriate supportive therapy as determined by the investigator in consultation with the medical monitor. Any AEs occurring as a result of an overdose should be reported to the medical monitor.

5.9 Occupational Safety

The investigational products are not expected to pose significant occupational safety risk to the study center personnel under normal conditions of use and administration. A material safety data sheet describing occupational hazards and recommended handling precautions will be provided to the investigator, where this is required by local laws, or will be available upon request from the sponsor.

6.0 CONCOMITANT MEDICATIONS AND NONDRUG THERAPIES

6.1 Permitted Medications

For prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted; treatment course should not last longer than 2 weeks and should be discussed with the medical monitor unless given for an immune-mediated reaction.

Patients with hematologic malignancies, particularly those having received prior lymphodepleting chemotherapy or having prolonged corticosteroid exposure, are pre-disposed to opportunistic infections as a result of disease and treatment-related factors. In patients with a high risk for opportunistic infections, including Pneumocystis jirovecii pneumonia (PJP), prophylaxis should be considered as per institutional standards.

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription medications, over-the-counter medications, herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date will also be included on the CRF.

All concomitant medications received within 28 days before the first dose of study medication and 28 days after the last infusion of study medication should be recorded.

The eCRF entry must include the dose, regimen, route, indication, and start and stop dates of use of the prior and concomitant medication.

6.2 Prohibited Medications

Subjects should not receive other anticancer therapy (cytotoxic, biologic, or hormone other than for replacement) while on treatment in this study. Other anticancer therapy should not be administered until disease progression (as per clinical practice standards at the study center), unmanageable toxicity, or no further clinical benefit occurs which requires permanent discontinuation of the investigational product. Bisphosphonate use is permitted if the subject has already been on it for 3 or more months and on a stable dose. Corticosteroid courses of limited duration (2 weeks or less) and dose (< 10 mg prednisone per day or equivalent) are permitted, if used to treat a concomitant (noncancer) medical condition. Corticosteroid treatment of longer duration for management of tislelizumab-related infusion reaction or immune-mediated AEs is permitted (see Section 6.3.2 and Section 9.14.2.4).

6.3 Medications to Be Used with Caution

6.3.1 Zanubrutinib

Administration of zanubrutinib with strong/moderate CYP3A inhibitors or CYP3A inducers (refer to Table 6-1 for a list of these medications) and grapefruit juice and Seville oranges should be used with caution as they may affect the metabolism of zanubrutinib. If at all possible, patients are encouraged not to use strong/moderate CYP3A inhibitors and inducers and consider using alternative agents. If these agents will be used, follow the dose modification table in Table 6-1. The medical monitor should be consulted in these situations. Please refer to http://medicine.iupui.edu/clinpharm/ddis/main-table/ for a more complete list.

Table 6-1 Dose Modification for Zanubrutinib when Co-Administered with Strong/Moderate CYP3A Inhibitors or Inducers

CYP3A	Co-administered Drug	Recommended use
Inhibition	Strong CYP3A inhibitor (eg, ketoconazole, conivaptan, clarithromycin, indinavir, itraconazole, lopinavir, ritonavir, telaprevir, posaconazole, voriconazole)	80 mg once daily
	Moderate CYP3A inhibitor (eg, erythromycin, ciprofloxacin, diltiazem, dronedarone, fluconazole, verapamil, aprepitant, imatinib, grapefruit products)	80 mg twice daily
Induction	Strong CYP3A inducer (eg, carbamazepine, phenytoin, rifampin, St. John's wort)	Avoid concomitant use; Consider alternative agents with less induction potential.
	Moderate CYP3A inducer (eg, bosentan, efavirenz, etravirine, modafinil, nafcillin)	160 mg twice daily, use with caution; Monitor for potential lack of efficacy.

Clinical drug-drug interaction study indicated that zanubrutinib is a mild inducer of CYP3A4 and CYP2C19 (Section 1.2). Narrow therapeutic index drugs that are metabolized by CYP3A4 (alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus), and CYP2C19 (eg, S-mephenytoin) should be used with caution, as zanubrutinib may decrease the plasma exposures of these drugs.

6.3.2 Tislelizumab

Subjects may be pretreated with H1 blockers (diphenhydramine 50 mg IV, or equivalent), and paracetamol (500 to 650 mg oral or IV), 30 to 60 minutes prior to each tislelizumab infusion.

Systemic corticosteroids required for the control of infusion reactions or AEs must be tapered and be at nonimmunosuppressive doses (≤ 10 mg/day of prednisone or equivalent) for at least 2 weeks before the next study drug administration (see Section 9.14.2.2 for further details). The use of steroids as prophylactic treatment for subjects with allergies to diagnostic imaging contrast dyes will be permitted.

7.0 SAFETY, PHARMACOKINETIC, EFFICACY, AND OTHER ASSESSMENTS

A signed, written informed consent must be obtained prior to screening assessments and **before** any study-specific assessments are initiated. The study-specific assessments and procedures are shown in Table 4-1 and Table 4-2, and the procedures schedule for pharmacokinetic sampling time points is presented in Table 4-3 and Table 4-4.

7.1 Screening: Demographic and Baseline Assessments

Having given consent, subjects will be required to undergo a medical screening to determine whether they are eligible to participate in the study according to the criteria in Section 4.2.1 and Section 4.2.2. Screening assessments will be performed within 28 days prior to Day 1 (first dosing) and will include the following:

- Demographic data (includes date of birth, race, height [cm], body weight [kg], and body mass index [kg/m^2])
- General medical history
- Vital signs
- B symptoms (unexplained weight loss > 10% over the previous 6 months, fever > 38ºC, and/or drenching night sweats)
- Complete physical examination
- ECOG performance status
- Echocardiogram or multigated acquisition (MUGA) scan
- 12-lead ECG
- Review of concomitant medications
- Hematology testing (Appendix 2)
- Clinical chemistry testing (Appendix 2)

- Coagulation parameters testing (Appendix 2)
- Urinalysis
- Pregnancy tests (for women of childbearing potential)
- IgA, IgG, and IgM level (Appendix 2)
- Viral serologies (HBV, HCV antibody, and human immunodeficiency virus [HIV])
- CT scan for tumor assessment
- MRI with gadolinium or CT with contrast of brain (Cohort 4 of expansion part only)
- Lumbar puncture or Ommaya tap for CSF analyses (Cohort 4 of expansion part only)
- Complete ophthalmologic examination with slit lamp (Cohort 4 of expansion part only)
- Ultrasound of testicle for male subjects with SCNSL of testicular origin and only if the positron emission tomography (PET)/CT scan is positive for testicular disease for Cohort 4 only
- Mammogram of bilateral breast for male or female subjects with SCNSL of breast origin for Cohort 4 only
- Bone marrow aspirations or biopsy
- CLL prognostic factors
- Archival tumor tissues
- Fresh tumor tissues (additional consent required)

The abovementioned data will be captured in the source documents. Any results outside the normal range, the test will be repeated at the discretion of the investigator.

7.1.1 Hepatitis B/C Testing

Hepatitis B/C serologic markers and/or viral load will be tested at screening. The hepatitis B testing includes HBsAg, HBcAb, and HBsAb as well as hepatitis B virus (HBV) DNA by polymerase chain reaction (PCR) if the subject is negative for HBsAg but HBcAb positive (regardless of HBsAb status). The hepatitis C testing includes hepatitis C virus (HCV) antibody as well as HCV RNA by PCR if the subject is HCV antibody positive. Subjects with positive HBsAg and/or detectable level of HBV DNA or detectable level of HCV RNA are not eligible. Subjects HBsAg negative, HBcAb positive and HBV DNA negative must undergo monthly HBV DNA screening PCR. If, during monthly monitoring of HBV DNA by PCR, the value is between

20 IU/mL and 100 IU/mL then the HBV DNA level should be rechecked within 2 weeks. Study drug should be held and anti-viral therapy initiated if the repeat level is between 20IU/mL and 100 IU/mL. If the HBV DNA by PCR is 100IU/mL or higher then study drug should be stopped and anti-viral therapy initiated. Subjects positive for HCV antibody but negative for HCV RNA must undergo monthly HCV RNA screening. Subjects with HIV infection are excluded from the study. Subjects with HCV RNA of 15 IU/mL or greater should stop study drug and anti-viral therapy should be initiated. The medical monitor should be informed of any suspected Hep B or Hep C reactivation and both tislelizumab and zanubrutinib should be held. Resuming either drug should only occur after discussion with the medical monitor; consultation with a specialist in hepatitis B may be also requested.

Table 7-1 shows how the results for HBV and HBV testing at screening relate to inclusion and exclusion criteria.

Table 7-1: Active Hepatitis B or Hepatitis C Infection (Detected Positive by Polymerase Chain Reaction)

Screening Assessment	**Meets Inclusion Criteria**	**To be Excluded**
HBV	**HBsAg (-) and HBcAb (-)**	**HBsAg (+)**
	HBsAg (-) *and* HBcAb (+) *HBV DNA "Not detected"* *Perform monthly monitoring of HBV DNA*	**HBsAg (-) *and* HBcAb (+)** *HBV DNA detected*
HCV	**Antibody (-) *or* Antibody (+)** *HCV RNA "Not-detected" (< 15 IU/mL)* *Perform monthly monitoring of HCV RNA*	**Antibody (+)** *HCV RNA Detected (≥ 15 IU/mL)*

HBsAg: Hepatitis B surface antigen; HBcAb: Hepatitis B core antibody; HBV: Hepatitis B virus; HCV: Hepatitis C virus; DNA: deoxyribonucleic acid; RNA: ribonucleic acid

7.1.2 Pulmonary Function Tests

Patients who are suspected or known to have serious/severe respiratory conditions or exhibit significant respiratory symptoms unrelated to the underlying cancer will undergo pulmonary function testing 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 on the study (refer to Section 4.1.3 for details).

7.2 Assessments During Treatment

Safety assessments should be performed at all visits to the study center and throughout the study. The list of events and the time when they will be performed is presented in Table 4-1 and Table 4-2.

7.2.1 Local Laboratory Evaluation

Laboratory assessments should be performed at a local certified laboratory (or a certified central laboratory if local laboratory is not feasible) on Day 1 before investigational product administration. Laboratory assessments need not be repeated on Day 1 if these assessments were completed for screening within 24 hours of the first administration. Required assessments are listed in Appendix 2.

Clinical chemistry, hematology, coagulation, urinalysis, and immunoglobulin, viral serologies, and thyroid function assessments will be performed at the time points specified in Table 4-1 and Table 4-2.

Clinical chemistry will include sodium, potassium, chloride, bicarbonate (total CO_2), glucose, urea, creatinine, calcium phosphorus, magnesium, total and direct bilirubin, total protein, albumin, ALT, AST, lactate dehydrogenase, alkaline phosphatase, and uric acid. In the event of ≥ Grade 3 clinical chemistry toxicity, these assessments will be conducted as frequently as the investigator feels needed until toxicity resolves to ≤ Grade 2.

Hematology will include red blood cell count, hemoglobin, reticulocyte count, white blood cell 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 (platelet count $< 50 \times 10^9$/L), these assessments will be conducted as frequently as the investigator 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.

For urinalysis, a urine dipstick will be collected as well as microscopy if the 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 occurrence.

Viral serologies should be performed during screening for all subjects. Viral serologies will include hepatitis B (HBsAg and total HB core antibody as well as HBV DNA by polymerase chain reaction if the subject is HB core antibody positive), HCV antibody (as well as HCV RNA by polymerase chain reaction if the subject is HCV antibody positive), and HIV.

Thyroid testing of T3, T4, and thyroid stimulating hormone will be performed at screening, then every other cycle starting from Cycle 2, and at the safety follow-up visit or early discontinuation visit. Additional T3, T4, and TSH may be performed at the discretion of the investigator.

Cerebrospinal fluid will be obtained by lumbar puncture and/or Ommaya tap in subjects with PCNSL or SCNSL of breast or testicular origin 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 lumbar puncture and Ommaya tap at suspected CR or unconfirmed complete response defined per for PCNSL or SCNSL. For subjects with CSF collection (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 plasma 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.

7.2.2 Physical Examination, Vital Signs, and B Symptoms

A complete or targeted physical examination, vital signs (systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate), weight, and B symptoms examination will be performed at the time points specified in Table 4-1 and Table 4-2.

Complete physical exam includes assessments of cardiovascular, respiratory, abdominal, and neurological systems as well as lymph nodes/spleen, skin, oropharynx, and extremities. 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.

7.2.3 Electrocardiogram and Cardiac Function

A 12-lead ECG in triplicate will be performed at screening and upon treatment completion or early termination visit and at the time points specified in Table 4-1, Table 4-2, Table 4-3, and Table 4-4. Note: not all required ECGs are indicated in these tables; additional ECGs may be required if there is a prolongation of QT or QTc (see below). If prolongation of QT or QTc is noted during the first 8 days, ECGs will be performed weekly during the first 2 cycles, and then on Day 1 every cycle onward for the remaining duration of treatment.

Significant QTc prolongation will be defined as an interval ≥ 500 msec (corrected based on the Fridericia's formula) or an interval that increases by ≥ 60 msec over baseline. Either of these

conditions should be documented on 2 or more ECG tracings separated by at least 5 minutes. The ECG tracing should be examined and a manual measurement by a trained physician should be performed to assess the accuracy of the equipment being used.

If a subject has significant QTc prolongation：

- The investigational product administration will be suspended.
- The subject will be medically assessed, treated appropriately, and closely followed until the QT and QTc interval returns to within 30 msec of baseline.
- The medical monitor will be consulted prior to administering further doses or rechallenging.
- The medical monitor will be consulted prior to administering higher doses.

An assessment of left ventricular ejection fraction (LVEF) will be performed and documented at screening and as medically indicated. Note: an echocardiogram or MUGA scan are acceptable.

7.2.4 Positron Emission Tomography (PET)-Computed Tomography (CT) and CT with Contrast Computed Tomography

Tumor 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, within 7 days of 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. That is, patients whose disease is not PET-avid will be followed by CT-based assessments alone while patients whose disease is PET-avid will be followed by an integration of PET-CT and CT-based assessments.

Ideally, contrast-enhanced CT should occur during a single visit combined with PET-CT. Combined PET-CT may be used in lieu of a CT with contrast only if the CT of the combined PET-CT has been performed with diagnostic quality and contrast is administered. An MRI may be used in place of CT only for patients who cannot undergo CT due to contrast allergy. All efforts will be made to ensure that the imaging equipment, contrast agent, and person (investigator or radiologist) performing the evaluation is kept constant throughout a patient's course on study. These images may be collected and reviewed by an independent review committee if required in the future.

7.2.5 Magnetic Resonance Imaging with Gadolinium of Brain

Tumor assessment by MRI with gadolinium of brain required for subjects in Cohort 4 of expansion per the schedule of assessments. A computed tomography scan with contrast of brain

may be substituted if MRI is contraindicated (eg, implanted metal or electronic device such as pacemaker or insulin pump, or claustrophobia).

7.2.6 Bone Marrow Evaluation

A bone marrow aspirate/biopsy must be performed at screening for all participants 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 assessments 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).

7.2.7 Ophthalmologic Examination

For all subjects, an eye exam, visual acuity test, and optical coherence tomography (or equivalent diagnostic test) will be assessed by an appropriate specialist at Screening. 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 or within 28 days of study drug initiation may be used for the Screening evaluation. Patients will undergo repeat assessments by an appropriate specialist approximately every 15 weeks (± 7 days) during study treatment and a final assessment < 30 days after the last dose of study treatment.

In addition, Investigators should solicit patients regarding changes in vision, visual disturbance, or ocular inflammation at each scheduled study visit during study treatment. For any change in vision, referral to an appropriate specialist will be made for further management guidance.

For subjects with PCNSL and SCNSL (Cohorts 4A and 4B), ophthalmologic examination as part of response criteria 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. Eye examinations performed for response evaluation do not need to be duplicated as part of the safety evaluations (specified above for all subjects) if they fall within the acceptable scheduling window for the safety-based eye exam, visual acuity test, and optical coherence tomography.

7.2.8 Ultrasound of Testicles

Ultrasound examination of the testicles is required for male subjects with SCNSL of testicular origin as per the schedule of assessments if the PET/CT scan is positive for testicular disease (Table 4-2).

7.2.9 Bilateral Breast Mammogram

Bilateral breast mammogram is required for male or female subjects with SCNSL of breast origin as per the schedule of assessments (Table 4-2).

7.2.10 Adverse Events

After informed consent has been signed but prior to the administration of the study drug, only SAEs should be reported. All AEs and SAEs, regardless of the relationship to the investigational product, will be collected from initiation of study drug and throughout the study.

7.2.11 Overall Disease Response Assessments

Overall response to study drug for each patient will be assessed using disease-standard criteria as specified in Appendix 4. Depending on disease, this assessment will incorporate several components listed in Section 7.2, including imaging, physical exam, laboratory evaluations, vital signs, bone marrow evaluation, and B-symptoms.

Response should be assessed against baseline unless otherwise noted by Appendix 4. Overall disease response will be used in assessments of study efficacy (Section 7.6).

7.3 Safety

Measurements used to evaluate safety will include vital signs, B symptoms, other signs and symptoms related to the disease or its treatment, clinical laboratory tests (hematology, clinical chemistry, coagulation, urinalysis, and immunoglobulin assessment), 12-lead ECG, physical examinations, and ECOG performance status. Throughout the study, the study center personnel will be monitoring AEs. Adverse events and toxicities will be graded according to NCI-CTCAE, Version 4.03.[20]

7.3.1 Safety Monitoring

The continuous safety monitoring will be performed by the investigators, the CRO medical monitors, and the sponsor. The SMC will be established for the evaluation of subjects' safety and determination of dose levels to be administered during dose escalation and the dose regimens in this study. Details of the safety monitoring process will be specified in a dedicated SMC charter.

The SMC consists of the coordinating investigator, selected recruiting investigators, the sponsor's medical monitor, and the contract research organization's (CRO) medical monitor. Ad hoc members will be consulted as needed and may include, but are not restricted to, the biostatistician and clinical pharmacologist.

7.3.1.1 SMC during Dose Escalation

Before moving to the next dose level, the SMC will review all safety data available to determine whether recruitment to the next cohort should be initiated. At the conclusion of the dose escalation, the SMC will determine the RP2Ds to be further investigated, based on the MTD and other relevant information.

The SMC will determine when no further dose escalation is appropriate and a RP2D is determined.

In dose escalation, the SMC will meet for cohort safety reviews after all subjects in a dosing level have completed the first treatment cycle. All available safety data will also be provided for subjects who discontinue prior to this time. Safety data from prior cohorts may also be presented. The decision to escalate dose and the determination of the RP2D will be based on the cohort safety reviews. The SMC will review any protocol violations that may have impacted evaluation of potential DLT. The SMC may weigh collective evidence and may determine a DLT for reasons in addition to those explicitly stated in the final protocol.

Response from all SMC members, including investigators with subjects enrolled in the study, or their designees, shall be required for each escalation/review.

Enrollment in subsequent dose levels will be put “on hold” during each review period, pending the decision of the SMC.

The SMC decision may fall into 1 of the categories detailed below:

- Escalate to a higher dose
- Recruit an additional 3 subjects into existing dose level
- Stop escalation and investigate lower dose(s)
- End part of the study
- End the overall study

Decisions will be made using the criteria defined within the protocol.

7.3.1.2 SMC during Dose Expansion

In the dose expansion, the SMC will meet at a minimum of every 6 months to review the safety status for all subjects enrolled or when there is a significant safety finding.

7.3.2 Pregnancy

7.3.2.1 Pregnancy Testing

A serum pregnancy test will be performed at screening in women of childbearing potential. Laboratory-based highly sensitive pregnancy tests (urine or serum) will be performed at specified subsequent visits. Pregnancy tests must be continued every 4 weeks (cycle) and for at least 90 days after the last dose of study drug (local laboratory assessment is acceptable after Safety Follow Up visit). If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Any subject who is pregnant will not be eligible for the study. A urine or serum pregnancy test must be performed if any woman suspects that she has become pregnant during the study.

The results of pregnancy tests will not be recorded in the database.

7.3.2.2 Time Period for Collecting Pregnancy Information

The time period for collecting information on whether a pregnancy occurs is every 4 weeks from screening to the 90 days after the last dose visit or early discontinuation from the study. Information on pregnancies identified prior to the investigational product administration does not need to be reported to the sponsor.

7.3.2.3 Action to Be Taken If a Pregnancy Occurs

A subject who has a positive pregnancy test result at any time after the investigational product administration will be immediately withdrawn from participation in the study. All post-study assessments will be collected at the time of discontinuation as described in Section 4.2.4.2.

The investigator or his/her designee will collect pregnancy information on any female subject or a female partner of a male subject who becomes pregnant while participating in this study. The investigator or his/her designee will record pregnancy information on the appropriate form and submit it to the sponsor within 2 weeks of learning of a subject's pregnancy. The subject will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE, as described in Section 9.7 and will be followed as described in Section 9.9.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 9.0. Furthermore, any SAE occurring as a result of a post-study pregnancy that is considered reasonably related to the investigational product by the investigator will be reported to

the sponsor as described in Section 9.12. While the investigator is not obligated to actively seek this information in former subjects, he/she may learn of an SAE through spontaneous reporting.

7.4 Safety Follow-up

Approximately 30 ± 3 days after the last administration of the investigational product, all subjects should return for a final evaluation. Assessments to be performed include vital signs, evaluation for B symptoms, targeted physical examination, ECOG performance status, 12-lead ECG, LVEF assessment (echocardiogram or MUGA), review of AEs, review of concomitant medications, laboratory tests (hematology, clinical chemistry, coagulation parameters, urinalysis, thyroid function, immunoglobulin, serum tumor markers (if appropriate), and tumor assessment by CT scan (if appropriate). In addition, 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, regardless of whether or not the patient starts a new anticancer therapy. Beyond 90 days, Investigators should continue to report any SAEs that are believed to be related to study drug(s) if they become aware of them.

Any abnormal finding of clinical consequence not related to the disease progression will be monitored until resolution or baseline status.

The same assessments for early discontinuation will be performed as for safety follow-up.

7.5 Efficacy Follow-up

Subjects who discontinue study drug due to reasons other than disease progression will remain on study and be followed every 3 months until subject exhibits first progression, starts new anti-cancer therapy, death, or study closure, whichever occurs first.

7.6 Survival Follow-up

Once subjects progress or start the use of alternative anti-cancer therapy, clinic visits are no longer required. Subjects only need to establish survival status every 3 months (telephone call, medical records, etc.).

7.7 Treatment Beyond Disease Progression

There is evidence that a minority of subjects treated with anti-PD1 therapies, such as tislelizumab, may derive clinical benefit despite initial documentation of PD by the response criteria in Section 14.0, Appendix 4.

Pseudo-progression may occur due to immune cell infiltration and other mechanisms, as manifested by apparent increase of existing tumor masses or appearance of new tumor lesions.

These subjects may go on to exhibit a partial response at a later time point. It is the responsibility of the investigator to determine if the subject should be considered for treatment beyond progression due to clinical benefit. This decision should be considered carefully so as to permit subjects who are likely to be benefitting to continue treatment while at the same time preventing prolonged exposure of a futile therapy in subjects who may not be benefitting. Any decisions to continue treatment beyond initial progression must be discussed with the medical monitor and documented in the study records.

Subjects with documented progression in tumor burden or the appearance of new lesions in the absence of significant clinical deterioration (decline in performance status and/or laboratory values) are permitted to continue with treatment until confirmation of PD with repeat imaging at least 4 weeks later or at the next regularly scheduled imaging time point. The next imaging to confirm disease progression must not exceed 12 weeks from initial documentation of PD.

If PD is suspected by the investigator to possibly reflect early pseudo-progression, subjects can be considered for treatment continuation until subsequent confirmation of PD as long as the following criteria are met:

- Absence of unmanageable clinical manifestations of toxicity (including worsening laboratory values)
- Stable ECOG performance status
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, cord compression) that necessitates urgent alternative medical intervention

7.8 Efficacy

Efficacy is not a primary objective of the study. Nevertheless, the following efficacy endpoints will be assessed:

- The number and proportion of subjects who achieve objective tumor response (CR, PR, and CR+PR) or SD
- PFS
- Overall survival (OS)
- Duration of response for responders (CR or PR) and duration of SD

Efficacy assessments will use the applicable response criteria with CT (or PET if applicable) for tumor assessments (see Section 7.2.4). Subjects who are at increased risk of allergic reaction to

iodinated contrast media should not have enhanced CT but should instead be provided MRI with gadolinium enhancement.

7.9 Pharmacokinetics

Blood in a subset of subjects will be collected to describe the PK profile of zanubrutinib and tislelizumab.

Blood samples for PK analysis will be collected at time points for zanubrutinib and for tislelizumab as described in Table 4-3 and Table 4-4. Total blood volume is presented in Appendix 3.

The actual time each sample was collected will be captured to the nearest minute in the eCRF and recorded in the database.

Details concerning handling of the PK blood samples, including labeling and shipping instructions, will be provided in the Study Manual.

Samples will be shipped to the central laboratory, where all samples will be analyzed for blood zanubrutinib and tislelizumab concentrations using validated methods.

For subjects with CSF collection (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 plasma zanubrutinib and serum tislelizumab concentrations will be collected at pre-dose (prior to zanubrutinib dose) and at 2 hours (+/- 10 minutes) post zanubrutinib dose.

7.10 Other Assessments

7.10.1 Archival/Fresh Tumor Tissue

Subjects with an accessible tumor lesion must agree to a fresh tumor biopsy at screening and another before the drug administration on Cycle 1 Day 8 (unless clinically unsafe), ideally taken from the same tumor lesion, for the biomarker analysis including but not limited to immunohistochemistry of PD-1, PD-L1, and T lymphocyte infiltration (up to first 12 qualified subjects). Written subject consent is required.

Subjects with DLBCL must have the archival tumor tissues or agree to a fresh tumor biopsy for confirmation of DLBCL subtype and biomarker analysis if they do not provide the tumor biopsies during screening. Written subject consent is required for collection of archival tumor tissue. Specific instructions for tissue collection and shipment are provided in the lab manual.

For the rest of subjects, upon consent (optional), an archival tumor tissue or a fresh tumor biopsy, if feasible, will be collected for the biomarker analysis. Upon consent, subjects who have disease relapse at any time will be asked to undergo rebiopsy of representative tumor sites to obtain samples for studying mechanisms of resistance. These studies may include phosphoprotein analysis of relevant pathways, whole exome or genome sequencing, and assessments of RNA expression.

7.10.2 Anti-Tislelizumab Antibodies

Immunogenic responses to tislelizumab combined with zanubrutinib will be assessed to determine occurrence of anti-drug antibody. Blood for anti-tislelizumab antibodies should be collected within 2 hours before start of infusion. Refer to Table 4-3 and Table 4-4 for details on the collection schedule. 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. Analysis will be performed by a central laboratory.

7.10.3 Biomarkers in the Blood

Other candidate biomarkers that will be investigated in the study may include, but are not limited to, proteomics and ctDNA profiling in peripheral blood. Specific instructions for sample collection and shipment are provided in the lab manual.

7.11 Appropriateness of Measurements

All safety and PK assessments used in this study are standard (i.e., widely used and generally recognized as reliable, accurate, and relevant).

8.0 QUALITY CONTROL AND QUALITY ASSURANCE

According to the International Conference on Harmonisation Note for Guidance on Good Clinical Practice, July 1996, the sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written Standard Operating Procedures (SOPs).

Quality control will be applied to each stage of data handling.

The following steps will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- Investigator meeting(s)
- Certified local laboratories for laboratory measurements and ECGs
- Study center initiation visit

- Early study center visits post-enrollment
- Routine study center monitoring
- Ongoing study center communication and training
- Data management quality control checks
- Continuous data acquisition and cleaning
- Internal review of data
- Quality control check of the final clinical study report

In addition, the sponsor and/or the CRO clinical quality assurance department may conduct periodic audits of the study processes, including, but not limited to, the study center, study center visits, central laboratories, vendors, clinical database, and the final clinical study report. When audits are conducted, access must be authorized for all study-related documents including medical history and concomitant medication documentation to authorized sponsor's representatives and regulatory authorities.

8.1 Monitoring

In accordance with applicable regulations, GCP, and sponsor procedures, the sponsor has engaged the services of a CRO to perform all monitoring functions within this clinical study. Monitors will work in accordance with the sponsor or CRO SOPs and have the same rights and responsibilities as monitors from the sponsor's organization. Monitors will establish and maintain regular contact between the investigator and the sponsor.

During these contacts, the monitor will:

- Check the progress of the study
- Review study data collected
- Conduct source document verification
- Identify any issues and address their resolution

This will be done in order to verify that the:

- Data are authentic, accurate, and complete
- Safety and rights of subjects are being protected

- Study is conducted in accordance with the currently approved protocol (and any amendments), GCP, and all applicable regulatory requirements

The investigator agrees to allow the monitor direct access to all relevant documents and to allocate his/her time and the time of his/her personnel to the monitor to discuss findings and any relevant issues.

At study closure, monitors will also conduct all activities described in Section 12.1.

8.2 Data Management/Coding

Data generated within this clinical study will be handled according to the relevant SOPs of the data management department of the CRO.

An electronic data capture system will be used for this study, meaning that all eCRF data will be entered in electronic forms at the study center. Data collection will be completed by authorized study center personnel designated by the investigator. Appropriate training and security measures will be completed with the investigator and all authorized study center personnel prior to the study being initiated and prior to any data being entered into the system for any subjects.

The eCRFs should always reflect the latest observations of the subjects participating in the study. Therefore, the eCRFs are to be completed as soon as possible during or after the subject's visit. To avoid interobserver variability, every effort should be made to ensure that the same individual who made the initial baseline determinations completes all safety evaluations. The investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available or not applicable or unknown, the investigator should indicate this in the eCRF. The investigator will be required to electronically sign off on the clinical data once complete.

The monitor will review the eCRFs and evaluate them for completeness and consistency. The eCRF will be compared with the source documents to ensure that there are no discrepancies between critical data. All entries, corrections, and alterations are to be made by the responsible investigator or his/her designee. The monitor cannot enter data in the eCRFs. Once clinical data have been entered into the eCRF, any corrections or alterations to the data fields will be traceable via an audit trail, meaning that the reason for change, the name of the person who performed the change, together with time and date will be logged. Roles and rights of the study center personnel responsible for entering the clinical data into the eCRF will be determined in advance. If additional corrections are needed, the responsible monitor or data manager will raise a query in the electronic data capture application. The appropriate study center personnel will respond to any queries raised.

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents used by the investigator or hospital that relate to the subject's medical history, that verify the existence of the subject, the inclusion and exclusion criteria, and all records covering the subject's participation in the study. They include laboratory notes, ECG results, memoranda, pharmacy dispensing records, subject files, etc.

The investigator is responsible for maintaining source documents. These will be made available for inspection by the study monitor at each monitoring visit. The investigator must submit a completed eCRF for each subject who receives the investigational product, regardless of the duration. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study and subject number. Any personal information, including subject name, should be removed or rendered illegible to preserve individual confidentiality.

Electronic CRF records will be automatically appended with the identification of the creator, by means of their unique user ID. Specified records will be electronically signed by the investigator to document his/her review of the data and acknowledgment that the data are accurate. This will be facilitated by means of the investigator's unique user ID and password; date and time stamps will be added automatically at the time of the electronic signature. If an entry on an eCRF requires change, the correction should be made in accordance with the relevant software procedures. All changes will be fully recorded in a protected audit trail, and a reason for the change will be required.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 17.0 or the latest version. Concomitant medications will be coded using the WHO Drug Dictionary. Concomitant diseases/medical history will be coded using the MedDRA Version 17.0 or the latest version.

8.3 Quality Assurance Audit

To ensure compliance with GCP and all applicable regulatory requirements, the sponsor may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her personnel to the auditor/inspector to discuss findings and any relevant issues.

9.0 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in this protocol. During the study, when there is a safety evaluation, the investigator or study center personnel will be responsible for detecting AEs and SAEs, as detailed in this section of the protocol. After informed consent has been signed but prior to the administration of the study drug, only SAEs should be reported. After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until 90 days after the last study treatment of the study drug, regardless of initiation of new anticancer therapy.

9.1 Definition of an Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational product.

Examples of an AE include:

- Worsening of a chronic or intermittent preexisting condition, including an increase in severity, frequency, duration, and/or that has an association with a significantly worse outcome
- New conditions detected or diagnosed after investigational product administration even though it may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication
- Significant failure of expected pharmacological or biological action. See Section 9.3 for additional information

Given that the mechanism of action by tislelizumab involves immune regulatory function, particular attention should be given to immune-related AEs, which include pruritus, vitiligo, pruritic rash, macular rash, hypopigmentation, other skin disorders, hypo- and hyperthyroidism, hypophysitis, pneumonitis, hepatitis, nephritis, allergic rhinitis, diarrhea, abdominal pain, fatigue, hypersensitivity, and any other immune-related AEs. For suspected immune-mediated adverse reactions, adequate evaluation should be ensured to confirm etiology or exclude other causes.

9.2 Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that, at any dose:

- Results in death
- Is life threatening

  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death, if it were more severe.

- Requires hospitalization or prolongation of existing hospitalization

  NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, or was necessary, the AE should be considered serious.

  Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline, or for social/logistical reasons only, is not considered an SAE.

- Results in disability/incapacity

  NOTE: The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect
- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition.

9.3 Lack of Efficacy

"Lack of efficacy" will not be reported as an AE. The signs and symptoms or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the AE or SAE definition (including clarifications).

9.4 Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Abnormal laboratory findings (eg, clinical chemistry, hematology, coagulation, urinalysis) or other abnormal assessments (eg, ECGs, X-rays, vital signs) that are judged by the investigator as clinically significant will be recorded as AEs, as defined in Section 9.1, or SAEs, as defined in Section 9.2. This includes clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen during the study. The definition of clinically significant is left to the judgment of the investigator; in general, these are the abnormalities that are associated with clinical signs or symptoms, require active medical intervention, or lead to dose interruption or discontinuation, or require close observation, or more frequent follow-up assessments, or further diagnostic investigation.

9.5 Time Period, Frequency, and Method of Detecting Adverse Events and Serious Adverse Events

9.5.1 Adverse Event Reporting Period

After informed consent has been signed but prior to the administration of the study drug, only SAEs should be reported.

After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until 90 days after the last study treatment of study drug, regardless of initiation of new anticancer therapy. After this period, the investigator should report any SAEs that are believed to be related to prior study drug treatment.

9.5.2 Eliciting Adverse Events

The investigator or designee will ask about AEs by asking the following standard questions:

- How are you feeling?
- Have you had any medical problems since your last visit?
- Have you taken any new medicines since your last visit?

9.6 Specific Instructions for Recording Adverse Events and Serious Adverse Events

9.6.1 Disease Progression

Disease progression (including fatal disease progression), which is expected in this study population and measured as an efficacy endpoint, should not be reported as an event term. Instead, the symptoms, signs or clinical sequelae that result from disease progression should be reported as the events.

For instance, a patient presents with pleural effusion resulting from disease progression of metastasis to lungs. The event term should be reported as “pleural effusion” instead of disease progression. If a patient experienced a fatal multi-organ failure due to disease progression, the term “multi-organ failure” should be reported as the SAE with death as outcome instead of reporting “fatal disease progression” or “death due to disease progression”.

9.6.2 Death

Death is an outcome and not usually considered an AE. If the only information available is death and the cause of death is unknown, then the death is reported as an event, e.g. “death”, “death of unknown cause”, or “death unexplained”.

9.7 Recording of Adverse Events and Serious Adverse Events

When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE or SAE in the eCRF. It is not acceptable for the investigator to send photocopies of the subject’s medical records to the sponsor in lieu of completion of the appropriate AE or SAE eCRF pages. However, there may be instances when copies of medical records for certain cases are requested by the sponsor. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to the sponsor.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE or SAE and not the individual signs/symptoms. Adverse events are independent components of the study.

9.8 Evaluating Adverse Events and Serious Adverse Events

9.8.1 Assessment of Severity

The investigator will make an assessment of severity for each AE and SAE reported during the study. When applicable, AEs and SAEs should be assessed and graded based upon NCI-CTCAE, Version 4.03. Subjects who initiate treatment with an absolute neutrophil count < 1000/μL will not be considered evaluable for neutrophil toxicity as outlined in the 2008 International Workshop on Chronic Lymphocytic Leukemia guidelines.[14]

Toxicities that are not specified in the NCI-CTCAE will be defined as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

NOTE: The terms “severe” and “serious” are not synonymous. Severity is a measure of intensity (for example, grade of a specific AE, mild [Grade 1], moderate [Grade 2], severe [Grade 3], or life threatening [Grade 4]), whereas seriousness is classified by the criteria based on the regulatory definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the sponsor to applicable regulatory authorities, as described in Section 9.2.

9.8.2 Assessment of Causality

The investigator is obligated to assess the relationship between the investigational product and the occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product will be considered and investigated. The investigator will also consult the IB and/or product information, for marketed products, in the determination of his/her assessment.

There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always makes an assessment of causality for every event prior to transmission of the SAE eCRF to the sponsor. The investigator may change his/her opinion of causality in light of follow-up

information, amending the SAE eCRF accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The causality of each AE should be assessed and classified by the investigator as "related" or "not related." An AE is considered related if there is at least "a reasonable possibility" that the AE may have been caused by the study drug (i.e., there are facts, evidence, or arguments to suggest possible causation, or a causal relationship between the AE and the drug cannot be ruled out). A number of factors should be considered in making this assessment, including:

- Temporal relationship of the AE to the administration of study treatment/study procedure
- Whether an alternative etiology has been identified
- Mechanism of action of the study drug
- Biological plausibility

An AE should be considered related to study drug if any of the following are met:

- There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
- There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
- There is some evidence to suggest a causal relationship (eg, the AE occurred within a reasonable time after administration of the study drug). However, the influence of other factors may have contributed to the AE (eg, the subject's clinical condition or other concomitant AEs).

An AE should be considered unrelated to study drug if any of the following are met:

- An unreasonable temporal relationship between administration of the study drug and the onset of the AE (eg, the AE occurred either before or too long after administration of the product for it to be considered product related)
- A causal relationship between the study drug and the AE is biologically implausible (eg, death as a passenger in an automobile accident)
- A clearly more likely alternative explanation for the AE is present (eg, typical adverse reaction to a concomitant drug and/or typical disease-related AE)

9.9 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE or SAE report, the investigator is required to proactively follow each subject and provide further information to the sponsor on the subject's condition. All AEs and SAEs documented at a previous visit/contact and are designated as ongoing will be reviewed at subsequent visits/contacts.

All AEs and SAEs will be followed until resolution, the condition stabilizes, the event is otherwise explained, the subject is lost to follow-up, or the subject withdraws consent. Once resolved, the appropriate AE or SAE eCRF page(s) will be updated. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

The sponsor may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obligated to assist. If a subject dies during participation in the study or during a recognized follow-up period, the sponsor will be provided with a copy of any postmortem findings, including histopathology.

New or updated information will be recorded on the originally completed SAE eCRF, with all changes signed and dated by the investigator. The updated SAE eCRF should be resent to the sponsor within the time frames outlined in Section 9.10.

9.10 Prompt Reporting of Serious Adverse Events

9.10.1 Timeframes for Submitting Serious Adverse Events

Serious adverse events will be reported promptly to the sponsor as described in Table 9-1 once the investigator determines that the event meets the protocol definition of a SAE.

Table 9-1 Timeframe for Reporting Serious Adverse Events to the Sponsor

Type of SAE	Initial SAE Report	Document	Follow-up SAE Report	Document
All SAEs	24 hours of investigator's knowledge	SAE eCRF	As soon as possible	Updated SAE eCRF

SAE: serious adverse event; eCRF: electronic case report form

9.10.2 Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a subject, he/she will report the information to the sponsor within 24 hours as outlined in Section 9.10.1. The SAE eCRF will always be completed as thoroughly as possible with all available details of the event, signed by the investigator (or designee), and forwarded to the sponsor within the designated timeframes. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying the sponsor of the event and completing the form. The form will be updated when additional information is received. The investigator will always provide an assessment of causality at the time of the initial report as described in Section 9.8.2.

In case the electronic data capture system is nonoperational, facsimile transmission of the SAE eCRF is the preferred method to transmit this information to the project contact for SAE receipt. In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE eCRF sent by overnight mail. Initial notification via the telephone does not replace the need for the investigator to complete and sign the SAE eCRF within the time frames outlined in Section 9.10.1. After the electronic data capture system becomes operational again, the investigator will enter the information in the system.

The sponsor will provide a list of project contacts for SAE receipt, fax numbers, telephone numbers, and mailing addresses.

9.11 Regulatory Reporting Requirements for Serious Adverse Events

The investigator will promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 9.10. The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the appropriate project contact for SAE receipt is essential so that legal obligations and ethical responsibilities toward the safety of other subjects are met.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

This protocol is being filed under an Investigational New Drug (IND) application with the U.S. FDA. Once active, a given SAE may qualify as an IND safety report if the SAE is both attributable to the investigational product and unexpected. In this case, all investigators filed to the IND (and associated INDs for the same compound) will receive an expedited investigator safety report, identical in content to the IND safety report submitted to the FDA.

Expedited investigator safety reports are prepared according to the sponsor's policy and are forwarded to investigators as necessary. Such a report is prepared for an SAE that is both attributable to investigational product and unexpected. The purpose of the report is to fulfill specific regulatory and GCP requirements regarding the product under investigation.

When a study center receives an initial or follow-up report or other safety information (eg, revised IB) from the sponsor, the responsible person according to local requirements is required to promptly notify his/her IRB or IEC.

9.12 Post-study Adverse Events and Serious Adverse Events

A post-study AE or SAE is defined as any event that occurs outside of the AE/SAE reporting period.

Investigators are not obligated to actively collect AEs or SAEs from former subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational product, the investigator will promptly notify the sponsor.

9.13 Serious Adverse Events Related to Study Participation

An SAE considered related to study participation (eg, procedures, invasive tests), even if it occurs during the post-treatment period, will be reported promptly to the sponsor (see Section 9.10).

9.14 Management of AE of Special Interest

9.14.1 Zanubrutinib

9.14.1.1 Tumor Lysis Syndrome

Subjects with a high tumor burden (circulating absolute lymphocyte counts ≥ 25×10^9/L or bulky lymphadenopathy) should receive prophylaxis for tumor lysis syndrome prior to the initiation of treatment. These subjects must be well hydrated. It is desirable to maintain a fluid intake of approximately 3 L per day, 1 to 2 days before the first dose of zanubrutinib. All such subjects with high tumor burden must be treated with allopurinol (≥ 300 mg/day orally) or a suitable alternative treatment (eg, rasburicase) starting at least 12 to 24 hours prior to the first dose of zanubrutinib. Subjects should continue to receive repeated prophylaxis with allopurinol and adequate hydration prior to each dosing, if deemed appropriate by the investigator.

9.14.1.2 Immune-related Adverse Events

Both zanubrutinib and tislelizumab should be held for immune-related events, regardless of causality.

- **Pneumonitis:** Monitor subjects for signs and symptoms of pneumonitis. Evaluate subjects with suspected pneumonitis with radiographic imaging and administer corticosteroids for Grade 2 or greater pneumonitis. Withhold zanubrutinib for moderate (Grade 2) pneumonitis: permanently discontinue zanubrutinib if the toxicity does not resolve within 12 weeks of last dose or with inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks. Permanently discontinue zanubrutinib for severe (Grade 3) or life-threatening (Grade 4) pneumonitis.

- **Colitis**: Monitor subjects for signs and symptoms of colitis. Administer corticosteroids for Grade 2 or greater colitis. Withhold zanubrutinib for moderate (Grade 2) or severe (Grade 3) colitis: permanently discontinue zanubrutinib if the toxicity does not resolve within 12 weeks of last dose or with inability to reduce corticosteroid to 10 mg or less of Prednisone or equivalent per day within 12 weeks. Permanently discontinue zanubrutinib for life-threatening (Grade 4) colitis.

Other tislelizumab immune-related holds: zanubrutinib should be held anytime tislelizumab is required to be held for an immune-related event (see Section 9.14.2.4). Zanubrutinib may be restarted after resolution of the event with approval of the medical monitor.

9.14.2 Tislelizumab

9.14.2.1 Tumor Lysis Syndrome

Treatment for tumor lysis syndrome is presented in Section 9.14.1.1.

9.14.2.2 Infusion-related Reactions

The symptoms of infusion-related reactions include fever, chills/rigor, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness or hypertension. Severe reactions may include acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. Patients should be closely monitored for such reactions. Immediate access to an intensive care unit (ICU) or equivalent environment and appropriate medical therapy (including epinephrine, corticosteroids, IV antihistamines, bronchodilators, and oxygen) must be available to treat infusion-related reactions.

Treatment modification for symptoms of infusion-related reactions due to study drug(s) is provided in Table 9-2.

Table 9-2 Treatment Modification for Symptoms of Infusion-Related Reactions Due to Study Drug(s)

NCI-CTCAE Grade	Treatment Modification for Tislelizumab
Grade 1 or 2 Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease infusion rate by 50%. Any worsening is closely monitored. Medical management as needed. Subsequent infusions should be given after premedication and at the reduced infusion rate.
Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs	Stop infusion. Infusion may be resumed at 50% of previous rate once infusion-related reactions has resolved or decreased to at least grade 1 in severity. Any worsening is closely monitored. Proper medical management should be instituted as described below. Subsequent infusions should be given after premedication and at the reduced infusion rate.
Grade 3 – severe Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae.	Immediately stop the infusion. Proper medical management should be instituted as described below. The patient should be withdrawn from study drug(s) treatment.
Grade 4 – life threatening Life-threatening consequences; urgent intervention indicated.	Immediately stop the infusion. Proper medical management should be instituted as described below. The patient should be withdrawn from study drug(s) treatment. Hospitalization is recommended.

Abbreviations: IV, intravenous; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Event; NSAIDs, nonsteroidal anti-inflammatory drugs.

Once the tislelizumab infusion rate has been decreased by 50% or suspended due to an infusion-related reaction, it must remain decreased for all subsequent infusions with premedication. If the patient has a second infusion-related reaction (≥ Grade 2) on the slower infusion rate, infusion should be discontinued and the patient should be withdrawn from tislelizumab treatment.

CTCAE Grade 1 or 2 infusion reaction: Proper medical management should be instituted, as indicated per type of the reaction. This includes but is not limited to an anti-histamine (eg, diphenhydramine or equivalent), anti-pyretic (eg, paracetamol or equivalent), and if considered indicated oral or IV glucocorticoids, epinephrine, bronchodilators, and oxygen. In the next cycle, patients should receive oral premedication with an antihistamine (eg, diphenhydramine or equivalent) and an antipyretic (eg, paracetamol or equivalent), and they should be closely monitored for clinical signs and symptoms of an infusion reaction.

CTCAE Grade 3 or 4 infusion reaction: Proper medical management should be instituted immediately, as indicated per type and severity of the reaction. This includes but is not limited to oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, and oxygen.

9.14.2.3 Severe Hypersensitivity Reactions and Flu-like Symptoms

If hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice as described in the complete guideline for emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (UK) (Soar et al 2008). Subjects should be instructed to report any delayed reactions to the investigator immediately.

In the event of a systemic anaphylactic/anaphylactoid reaction (typically manifested within minutes following administration of the drug/antigen and characterized by respiratory distress; laryngeal edema; and/or intense bronchospasm [often followed by vascular collapse or shock without antecedent respiratory difficulty]; cutaneous manifestations such as pruritus and urticaria with/without edema; and gastrointestinal manifestations such as nausea, vomiting, crampy abdominal pain, and diarrhea), the infusion must be immediately stopped and the subject discontinued from the study drug.

Subjects will be administered with epinephrine injection and dexamethasone infusion if hypersensitivity reaction is observed, and then the subject should be placed on monitor immediately and ICU alerted for possible transfer if needed.

For prophylaxis of flu-like symptoms, a dose of 25 mg indomethacin or a comparable dose of nonsteroidal anti-inflammatory drugs (ie, 600 mg ibuprofen, 500 mg naproxen sodium) may be administered 2 hours before and 8 hours after the start of each dose of tislelizumab IV infusion. Alternative treatments for fever (i.e., paracetamol) may be given to subjects at the discretion of the investigator.

9.14.2.4 Immune-related Adverse Events

Immune-related AEs are of special interest in this study. If the events listed below or similar events occur, the investigator should exclude alternative explanations (eg, combination drugs, infectious disease, metabolic, toxin, disease progression or other neoplastic causes) with appropriate diagnostic tests, which may include but is not limited to serologic, immunologic, and histologic (biopsy) data. If alternative causes have been ruled out; the AE required the use of systemic steroids, other immunosuppressants, or endocrine therapy and is consistent with an immune mediated mechanism of action, the irAE indicator in the eCRF AE page should be checked.

A list of potential irAEs is shown below in Table 9-3. All conditions similar to those listed should be evaluated in patients receiving tislelizumab tislelizumab to determine whether they are immune-related.

Recommendation for diagnostic evaluation and management of irAEs is based on a recent ESMO guideline (Haanen et al 2017) and common immune-related toxicities are detailed in Appendix 6. For any adverse events not included in Appendix 6, please refer to the recent ESMO guideline (Haanen et al 2017) for further guidance on diagnostic evaluation and management of immune-related toxicities.

Table 9-3 Immune-Related Adverse Events

Body System Affected	Events
Skin (mild-common)	pruritus or maculopapular rash; vitiligo
Skin (moderate)	follicular or urticarial dermatitis; erythematous/lichenoid rash; Sweet's syndrome
Skin (severe-rare)	full-thickness necrolysis/Stevens-Johnson syndrome
Gastrointestinal	colitis (includes diarrhea with abdominal pain or endoscopic/radiographic evidence of inflammation); pancreatitis; hepatitis; aminotransferase (ALT/AST) elevation; bowel perforation
Endocrine	thyroiditis, hypothyroidism, hyperthyroidism; hypophysitis with features of hypopituitarism, eg, fatigue, weakness, weight gain; insulin-dependent diabetes mellitus; diabetic ketoacidosis; adrenal insufficiency
Respiratory	pneumonitis/diffuse alveolitis
Eye	episcleritis; conjunctivitis; iritis/uveitis
Neuromuscular	arthritis; arthralgia; myalgia; neuropathy; Guillain-Barre syndrome; aseptic meningitis; myasthenic syndrome/myasthenia gravis, meningoencephalitis; myositis
Blood	anemia; leukopenia; thrombocytopenia
Renal	interstitial nephritis; glomerulonephritis; acute renal failure
Cardiac	pericarditis; myocarditis; heart failure

Dose modification and management for irAEs are detailed in Appendix 6.

If a toxicity does not resolve to ≤ Grade 1 within 12 weeks, study drug(s) should be discontinued after consultation with the sponsor. Patients who experience a recurrence of any event at the same or higher severity grade with rechallenge should permanently discontinue treatment.

9.15 Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Ethics Committees

The sponsor will promptly assess all SAEs against cumulative study drug experience to identify and expeditiously communicate new safety findings to regulatory authorities, investigators, IRBs, and IECs based on applicable legislation.

To determine the reporting requirements for individual SAEs, the sponsor will assess the expectedness of the SAEs using the following reference documents:

- Zanubrutinib (BGB-3111) Investigator's Brochure
- Tislelizumab (BGB-A317) Investigator's Brochure

10.0 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

10.1 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.

10.2 General Considerations for Data Analysis

Complete details will be documented in the reporting and statistical analysis plan.

10.2.1 Analysis Set

The following analysis sets will be analyzed:

All subjects enrolled set (ENR): Includes all subjects who provide informed consent for this study. The ENR analysis set will be used to summarized and describe the subject disposition, deaths, unless stated otherwise.

Safety analysis set (SAF): Includes all subjects in the ENR set who receive at least 1 dose of zanubrutinib and/or tislelizumab. The SAF analysis set will be used for all summaries (except DLTs).

DLT analysis set (DLTS): Includes all subjects who 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.

PK analysis set (PKS): Includes subjects who have received at least the first dose of tislelizumab plus zanubrutinib and provided PK samples as per protocol following first dosing on Day 1.

10.2.2 Interim Analysis

No formal interim analysis is planned for this study. Since this is a dose escalation study, safety, PK, and preliminary efficacy data will be evaluated on an ongoing basis.

10.2.3 Withdrawal

Subjects who dropout will be replaced whenever possible.

10.3 Efficacy Analyses

The responses will be assessed using the applicable response criteria in Appendix 4. Objective response rates will be determined along with 95% confidence intervals.

Progression free survival and OS are defined as the time from first dose of zanubrutinib, to disease progression, or death. Kaplan-Meier methodology will be used to estimate median PFS and OS and 95% confidence interval. Kaplan-Meier curves will be constructed to provide a visual description of the PFS and OS change with time.

All subjects who take investigational products and have a baseline tumor assessment will be included in the efficacy analysis set.

Study drug exposure data, including the number of cycles using study drug and dose intensity, will be summarized.

10.3.1 Primary Analysis

Safety will be assessed by monitoring and recording of all AEs graded by NCI-CTCAE, Version 4.03, and laboratory values (eg, hematology, clinical chemistry, urinalysis). Vital signs and physical examinations will also be used in determining safety. Descriptive statistics will be used to analyze all safety data by study part (dose escalation vs. dose expansion) in the SAF. In the dose escalation, DLT will be summarized at each dosing cohort in the DLT set. Maximum tolerated dose may not be reached in the 4 planned dose levels. RP2D will be determined based on overall safety profile of each dose level. In the dose expansion part, efficacy and safety will be summarized by cohort and overall.

10.3.2 Efficacy Analysis

The secondary efficacy endpoints, including ORR, DOR, and PFS, will be summarized by part and by cohort within dose expansion part, in the clinical study report (CSR).

Objective response rate and its binomial exact 95% confidence interval will be calculated.

Duration of response and PFS will be estimated using the Kaplan-Meier method. Its 95% confidence interval will be constructed using Greenwood's formula. Duration of response and PFS censoring rule will follow US FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007). Only subjects who have achieved objective responses will be included in the analysis of DOR.

Kaplan-Meier curves of DOR and PFS in each dose expansion cohort will be plotted and percentages of maximum decrease of sum of target lesions in each subject will be calculated and displayed in waterfall plots.

PK samples will be collected in this study, and PK analyses are detailed in Section 10.5.

Incidence of development of anti-drug antibody to tislelizumab and its 95% confidence interval will be summarized.

10.3.3 Exploratory Analysis

[redacted]

10.4 Safety Analyses

All subjects who are exposed to zanubrutinib and/or tislelizumab will be evaluated for safety.

Adverse event rates and changes in laboratory results by dose levels will be summarized in tabular form. Adverse events representing clear evidence of disease progression will not be considered relevant to the assessment of toxicity.

Adverse events and toxicities will be graded according to NCI-CTCAE, Version 4.03. Subjects who initiate treatment with an absolute neutrophil count < 1000/μL will not be considered evaluable for neutrophil toxicity as outlined in the 2008 International Workshop on Chronic Lymphocytic Leukemia Guidelines.[14]

Summaries of the number of toxicity grades for both laboratory and nonlaboratory data will be presented by dose levels. Adverse events of special interest will be defined in the statistical analysis plan.

Hematology, clinical chemistry, coagulation, and urinalysis values will be listed for each subject and flagged as high or low relative to the normal range, where applicable. Predose values will be used to assess laboratory shifts occurring at postdose. A comparison of prestudy and poststudy values will be performed to identify any parameters that have not returned to prestudy levels.

Adverse events will be coded and grouped using the MedDRA Version 17.0 or the latest version. All AEs will be listed.

10.4.1 Extent of Exposure

Extent of exposure to zanubrutinib and/or tislelizumab will be calculated for each subject. Overall exposure will also be summarized by dose levels.

10.4.2 Electrocardiogram

All ECG parameters, including the QT interval corrected for heart rate (QTc), will be listed for each subject and summarized by dose level and assessment time. Change from baseline will also be summarized. The relationship between dose level and QTc changes will be explored by graphs. The QTc will be calculated using Fridericia's formula.

10.5 Pharmacokinetics Analyses

For dose escalation cohorts (zanubrutinib PK data collected on C1D1 and C2D1), PK parameters of zanubrutinib will be derived using standard noncompartmental methods with WinNonlin Professional, Version 5.2 or higher (Pharsight Corp., Mountain View, CA). Nominal sampling times will be used for interim PK parameter calculations, while actual sampling times will be used in the final PK parameter calculations. Sampling times are displayed in Table 4-3 and Table 4-4. Sparse PK data of tislelizumab in dose escalation and sparse PK data of zanubrutinib and tislelizumab in dose expansion will be used in the PK analysis set and will be reported separately.

For subjects with PCNSL or SCNSL only (Cohort 4 of Expansion Phase), CSF obtained by lumbar puncture and/or Ommaya tap (at end of Cycles 2, 6 and 12), may be assessed for measurement of zanubrutinib and tislelizumab concentrations. On the same day of CSF collection, blood samples for measuring zanubrutinib and serum tislelizumab concentrations will be collected at pre-dose (prior to zanubrutinib dose) and at 2 hours (+/- 10 minutes) post zanubrutinib dose. See Table 4-4 for additional details on collection procedures and times.

$AUC_{0\text{-infinity}}$ Area under the plasma concentration-time curve from zero extrapolated to infinity calculated using the linear up/log down trapezoidal method

AUC_{last} and AUC_{ss}	Area under the plasma concentration-time curve from zero to the last quantifiable concentration
C_{max} and $C_{max,ss}$	Maximum plasma concentration
t_{max} and $t_{max,ss}$	Time of maximum plasma concentration
λ_z	Terminal rate constant
$t_{1/2}$	Terminal half-life
CL/F	Apparent systemic plasma clearance
V_z/F	Apparent volume of distribution during the terminal phase
RAUC	AUC accumulation ratio (AUC Cycle 2 Day 1/AUC Cycle 1 Day 1)
RC_{max}	C_{max} accumulation ratio (C_{max} Week 2 Day 1/C_{max} Week 1 Day 1)

Where possible, the following diagnostic parameters of the plasma PK analysis will be calculated and listed, but not summarized:

Interval	The time interval (hours) of the log-linear regression used to determine λ_z
n	Number of data points included in the log-linear regression analysis to determine λ_z (a minimum of 3 points will be used)
Rsq	R-square; coefficient of determination for calculation of λ_z. If Rsq is < 0.800, then λ_z and related parameters will not be reported
$\%AUC_{ex}$	Percentage of AUC obtained by extrapolation; if > 20%, then AUC and related parameters will not be reported

Blood zanubrutinib and tislelizumab concentration-time data will be summarized and displayed in both tabular and graphical form. Concentration-time data will be analyzed with standard noncompartmental and/or compartmental PK methods. The PK parameters for a single dose profile (AUC_{last}, AUC, C_{max}, t_{max}, $t_{1/2}$, CL/F, and V_d/F) and after steady-state ($AUC_{last,ss}$, $C_{max,ss}$, $t_{max,ss}$), will be calculated, if there are sufficient data. Individual subject parameter values, as well as a descriptive summary (mean, standard deviation, median, minimum, maximum, and the standard deviation and geometric mean of log-transformed parameters) by treatment group will be reported. Individual subject parameter values will be plotted against dose.

In the dose escalation, C_{max}, C_{trough}, T_{max}, AUC_{last} or other applicable PK parameters for zanubrutinib may be derived for each cycle at which pharmacokinetics are to be measured; C_{trough} may be derived for tislelizumab, where applicable (as specified in Table 4-3). In the dose

expansion part of the study, PK parameters such as C_{trough} may be derived for both zanubrutinib and tislelizumab for each cycle at which pharmacokinetics are to be measured, where applicable (as specified in Table 4-4).

Additional PK analyses will be conducted as appropriate in all subjects for whom valid tislelizumab and zanubrutinib PK parameters can be estimated.

Summary statistics of the calculated PK parameters will be provided. Graphical, noncompartmental and [redacted].

10.6 Immunogenicity Analyses

Samples to assess anti-tislelizumab antibodies will be collected in patients receiving tislelizumab and in sites that are able to adequately perform sampling, handling and processing procedures outlined in the Laboratory Manual.

The immunogenicity results will be summarized using descriptive statistics by the number and percentage of patients who develop detectable ADAs. The incidences of positive ADAs and neutralizing ADAs will be reported for evaluable patients. The effect of immunogenicity on PK, efficacy, and safety may be evaluated if data allow.

10.7 Biomarker Analyses

Clinical response to zanubrutinib and tislelizumab will be evaluated for possible correlation with established genomic and clinical risk factors.

The primary predictive biomarker analysis is based on a subset of the subjects with both a valid PD-L1 expression and/or TIL measurement and at least 1 disease assessment post-treatment. A supportive analysis is based on subjects with a valid PD-L1 expression and/or TIL measurement, irrespective of the availability of post-treatment disease assessments. In this analysis, those without post-treatment disease assessments will be imputed with the worst outcome in tumor

response. [redacted]

For subjects with paired tumor biopsies, changes in the tumor tissues, including but not limited to PD-L1 expression and TIL levels, following zanubrutinib treatment will be analyzed.

11.0 ETHICS

11.1 Regulatory Authority Approval

The sponsor will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements before the study is initiated at a study center in that country.

11.2 Ethical Conduct of the Study and Ethics Approval

This study will be conducted in accordance with GCP and all applicable regulatory requirements, including, where applicable, current version of the Declaration of Helsinki.

The investigator (or sponsor, where applicable) is responsible for ensuring that this protocol, the study center's informed consent form, and any other information that will be presented to potential subjects (eg, advertisements or information that supports or supplements the informed consent) are reviewed and approved by the appropriate IEC/IRB. The investigator agrees to allow the IEC/IRB direct access to all relevant documents. The IEC/IRB must be constituted in accordance with all applicable regulatory requirements. The sponsor will provide the investigator with relevant documents/data that are needed for IEC/IRB review and approval of the study. Before the investigational products can be shipped to the study center, the sponsor must receive copies of the IEC/IRB approval, the approved informed consent form, and any other information that the IEC/IRB has approved for presentation to potential subjects.

If the protocol, the informed consent form, or any other information that the IEC/IRB has approved for presentation to potential subjects is amended during the study, the investigator is responsible for ensuring the IEC/IRB reviews and approves, where applicable, these amended documents. The investigator must follow all applicable regulatory requirements pertaining to the use of an amended informed consent form including obtaining IEC/IRB approval of the amended form before new subjects consent to take part in the study using this version of the form. Copies of the IEC/IRB approval of the amended informed consent form/other information and the approved amended informed consent form/other information must be forwarded to the sponsor promptly.

11.3 Informed Consent

Informed consent will be obtained before the subject can participate in the study. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements.

11.4 Investigator Reporting Requirements

As indicated in Section 9.10, the investigator (or sponsor, where applicable) is responsible for reporting SAEs to the IEC/IRB, in accordance with all applicable regulations. Furthermore, the investigator may be required to provide periodic safety updates on the conduct of the study at his/her study center and notification of study closure to the IEC/IRB. Such periodic safety updates and notifications are the responsibility of the investigator and not of the sponsor.

12.0 STUDY ADMINISTRATION

12.1 Study and Study Center Closure

Study closure is anticipated to occur approximately 1 year following initiation of the last study subject. Upon completion of the study, the monitor will conduct the following activities in conjunction with the investigator or study center personnel, as appropriate:

- Return of all study data to the sponsor
- Data queries
- Accountability, reconciliation, and arrangements for unused investigational products
- Review of study records for completeness
- Return of treatment codes to the sponsor
- Shipment of PK samples to assay laboratories

In addition, the sponsor reserves the right to temporarily suspend or prematurely discontinue this study either at a single study center or at all study centers at any time for reasons including, but not limited to, safety or ethical issues or severe noncompliance. If the sponsor determines such action is needed, the sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. When feasible, the sponsor will provide advance notification to the investigator of the impending action prior to it taking effect.

The sponsor will promptly inform all other investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If

required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must be returned to the sponsor. In addition, arrangements will be made for all unused investigational products in accordance with the applicable sponsor procedures for the study.

Financial compensation to investigators and/or institutions will be in accordance with the agreement established between the investigator and the sponsor.

12.2 Records Retention

Following closure of the study, the investigator must maintain all study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval when needed (eg, audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and personnel. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (eg, microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible, are a true and accurate copy of the original, and meet accessibility and retrieval standards, including regenerating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back up of these reproductions and that an acceptable quality control process exists for making these reproductions.

The sponsor will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that study center for the study, as dictated by any institutional requirements or local laws or regulations, or the sponsor's standards/procedures; otherwise, the retention period will default to 15 years.

The investigator must notify the sponsor of any changes in the archival arrangements, including, but not limited to archival at an off-site facility and transfer of ownership of the records in the event the investigator leaves the study center.

12.3 Provision of Study Results and Information to Investigators

When the clinical study report is completed, the sponsor will provide the major findings of the study to the investigator.

In addition, details of the study treatment assignment will be provided to the investigator to enable him/her to review the data to determine the outcome of the study for his/her subjects.

The sponsor will not routinely inform the investigator or subject of the test results because the information generated from this study will be preliminary in nature, and the significance and scientific validity of the results will be undetermined at such an early stage of research.

12.4 Information Disclosure and Inventions

All information provided by the sponsor and all data and information generated by the study center as part of the study (other than a subject's medical records) is the sole property of the sponsor. This will be determined by the sponsor as other details on publications are provided.

All rights, title, and interests in any inventions, know-how or other intellectual or industrial property rights which are conceived or reduced to practice by the study center personnel during the course of or as a result of the study are the sole property of the sponsor, and are hereby assigned to the sponsor.

If a written contract for the conduct of the study which includes ownership provisions inconsistent with this statement is executed between the sponsor and the study center, that contract's ownership provisions shall apply rather than this statement.

All information provided by the sponsor and all data and information generated by the study center as part of the study (other than a subject's medical records) will be kept confidential by the investigator and other study center personnel. This information and data will not be used by the investigator or other study center personnel for any purpose other than conducting the study without the prior written consent of the sponsor.

These restrictions do not apply to:

- Information that becomes publicly available through no fault of the investigator or study center personnel
- Information that is necessary to disclose in confidence to an IEC/IRB solely for the evaluation of the study
- Information that is necessary to disclose in order to provide appropriate medical care to a subject
- Study results that may be published

If a written contract for the conduct of the study which includes provisions inconsistent with this statement is executed, that contract's provisions shall apply rather than this statement.

12.4.1 Study Report and Publication Policy

A clinical study report will be prepared and provided to the regulatory agency(ies). BeiGene will ensure that the report meets the standards set out in the International Conference on Harmonisation Guideline for Structure and Content of Clinical Study Reports (International Conference on Harmonisation E3). Note that an abbreviated report may be prepared in certain cases.

The results of this study will be published or presented at scientific meetings in a timely, objective, and clinically meaningful manner that is consistent with good science, industry and regulator guidance, and the need to protect the intellectual property of BeiGene (sponsor), regardless of the outcome of the trial. The data generated in this clinical trial are the exclusive property of the sponsor and are confidential. As this is a multicenter study, the first publication or disclosure of study results shall be a complete, joint multicenter publication or disclosure coordinated by the sponsor. Thereafter, any secondary publications will reference the original publication(s). Authorship will be determined by mutual agreement, and all authors must meet the criteria for authorship established by the International Committee of Medical Journal Editors Uniform Requirements for Manuscripts or stricter local criteria (International Committee of Medical Journal Editors, 2013).

Each investigator agrees to submit all manuscripts, or congress abstracts, and posters, publications, and presentations (both oral and written) to the sponsor for review before submission or presentation in accordance with the clinical study agreement. This allows the sponsor to protect proprietary information, provide comments based on information from other studies that may not yet be available to the investigator, and ensure scientific and clinical accuracy. Each investigator agrees that, in accordance with the terms of clinical study agreement, a further delay of the publication/presentation may be requested by the sponsor to allow for patent filings in advance of the publication/presentation.

13.0 REFERENCES

1. Rickert RC. New insights into pre-BCR and BCR signaling with relevance to B cell malignancies. Nat Rev Immunol 2013. 13(8):578-91.

2. Advani, RH et al. Bruton tyrosine kinase inhibitor ibrutinib ((PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies. J Clin Oncol 2013; 31(1):88-94.

3. Ibrutinib approved for mantle cell lymphoma. Cancer Discov, 2014, 4(1):OF1.

4. Ibrutinib (Imbruvica) for chronic lymphocytic leukemia. Med Lett Drugs Ther, 2014; 56(1440): 29-30.

5. Byrd JC et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med 2013:369(1):32-42.

6. Wang ML, et al., Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. N Engl J Med 2013; 369(6):507-16.

7. McDermott DF, Atkins M B, PD-1 as a potential target in cancer therapy. Cancer Med 2013; 2(5):662-73.

8. Hawkes EA, Grigg A, Chong G. Programmed cell death-1 inhibition in lymphoma. Lancet Oncol 2015; 16(5):e234-e245.

9. Westin JR, Chu F, Zhang M, et al. Safety and activity of PD1 blockade by pidilizumab in combination with rituximab in patients with relapsed follicular lymphoma: a single group, open-label, phase 2 trial. Lancet Oncol 2014;15: 69–77.

10. Lesokhin AM, Ansell SM, Armand P, et al. Preliminary results of a phase I study of nivolumab (BMS-936558) in subjects with relapsed or refractory lymphoid malignancies. Blood 2014; 124:Abstr 291.

11. Moskowitz CH, Ribrag V, Michot J-M, et al. PD-1 blockade with the monoclonal antibody pembrolizumab (MK-3475) in patients with classical Hodgkin lymphoma after brentuximab vedotin failure: preliminary results from a phase 1b study (KEYNOTE-013). Blood 2014; 124:Abstr 290.

12. Brahmer JR, Drake CG, Wollner I, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol 2010; 28(19):3167-75.

13. Topalian SL, Hodi F S, Brahmer JR, et al., Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med, 2012; 366(26):2443-54.

14. Hallek M 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(12):5446-556.

15. Hamid O, Robert C, Daud A, et al., Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. N Engl J Med, 2013; 369(2):134-44.

16. Wolchock JD et al. Nivolumab plus ipilumumab in advanced melanoma. N Engl J Med 2013; 369(2):122-33.

17. Keytruda (pembrolizumab) [package insert]. Whitehouse, NJ: Merck, 2014.

18. Opdivo (nivolumab) [package insert]. Princeton, NJ: Bristol-Myers Squibb, 2014.

19. Bai et al. 2012

20. US Department of Health and Human Services, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. Washington, DC. 14 June 2010.

21. Cheson BD; International Harmonisation Project on Lymphoma**.** Revised response criteria for malignant lymphoma. J Clin Oncol 2007; 25(5):579-86.

22. Abrey LE, Batchelor TT, Ferreri AJM, et al., Report of an International Workshop to Standardize Baseline Evaluation and Response Criteria for Primary CNS Lymphoma. J Clin Oncol 2005;23(22):5034-43.

14.0 APPENDICES

APPENDIX 1: SIGNATURE OF INVESTIGATOR

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

PROTOCOL NO: BGB-3111_BGB-A317_Study_001

This protocol is a confidential communication of BeiGene Aus Pty Ltd. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene Aus Pty Ltd.

Instructions to the investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the center in which the study will be conducted. Return the signed copy to PAREXL International.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

_____

APPENDIX 2: 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

ALT = alanine aminotransferase; AST = aspartate aminotransferase;LDH = lactate dehydrogenase; TSH = thyroid stimulating hormone; WBC = white blood cell.

[a] On routine urinalysis, if urine protein is ≥ 2+ by dipstick, then obtain a 24-hour urine sample (on the first occurrence) for total protein and a random urine sample for total protein and creatinine to determine a protein to creatinine ratio.

[b] Only for subjects with primary or secondary central nervous system lymphoma of breast or testicular origin (Cohort 4 of expansion part).

APPENDIX 3: BLOOD REQUIREMENTS

Blood Requirements for Safety Evaluation of Zanubrutinib in Combination with Tislelizumab During Dose Escalation

Time point	Assessment	Total blood volume (mL)
Screening		
	Clinical chemistry	5
	Hematology	2.5
	Coagulation	3
	Thyroid function	3
	IgA, IgG, and IgM level	5
	Pregnancy test	3.5
	Virology	5
	CLL prognostic factors	5
	Total	**32**
Cycle 1, Day 1		
	Clinical chemistry	5
	Hematology	2.5
	Coagulation	3
	PK for zanubrutinib (5 samples @ 4 mL each)	20
	Total	**30.5**
Cycle 1, Day 2		
	Clinical chemistry	5
	Hematology	2.5
	PK for zanubrutinib (1 sample @ 4 mL)	4
	Clinical chemistry	5
	Hematology	2.5
	Anti-tislelizumab	2
	Total	**9.5**
Cycle 1, Day 15		
	Clinical chemistry	5
	Hematology	2.5
	Total	**7.5**
Cycle 1, Day 22		
	Clinical chemistry	5
	Hematology	2.5
	Total	**7.5**
Cycle 2, Day 1		
	Clinical chemistry	5
	Hematology	2.5
	Coagulation	3
	IgA, IgG, and IgM level	5
	Thyroid function	3
	Anti-tislelizumab	2
	PK for zanubrutinib (5 samples @ 4 mL each)	20
	PK for tislelizumab (2 samples @ 5 mL each)	10
	Total	**50.5**

Time point	Assessment	Total blood volume (mL)
Cycle 3, Day 1		
	Clinical chemistry	5
	Hematology	2.5
	Coagulation	3
	IgA, IgG, and IgM level	5
	Thyroid function	3
	PK for tislelizumab (2 samples @ 5 mL each)	10
	Total	**28.5**
Cycle 4, Day 1		
	Clinical chemistry	5
	Hematology	2.5
	Coagulation	3
	IgA, IgG, and IgM level	5
	Thyroid function	3
	Anti-tislelizumab	2
	PK for tislelizumab (2 samples @ 5 mL)	10
	Total	**30.5**
Cycle 5+, Day 1		
	Clinical chemistry	5
	Hematology	2.5
	Coagulation	3
	IgA, IgG, and IgM level	5
	Thyroid function	3
	Anti-tislelizumab[1]	2
	Total	**20.5**
Safety Follow-up		
	Clinical chemistry	5
	Hematology	2.5
	Coagulation	3
	IgA, IgG, and IgM	5
	Thyroid function	3
	Anti-tislelizumab	2
	Total	**20.5**
Survival Follow-up		
	Clinical chemistry	5
	Hematology	2.5
	IgA, IgG, and IgM level	5
	Total	**12.5**

PK = pharmacokinetic

[1] Blood samples will be collected on Day 1 of Cycles 6, 8, 12, and 16.

Blood Requirements for Safety Evaluation of Zanubrutinib in Combination with Tislelizumab During Dose Expansion

Time point	Assessment	Total blood volume (mL)
Screening		
	Clinical chemistry	5
	Hematology	2.5
	Coagulation	3
	Thyroid function	3
	IgA, IgG, and IgM level	5
	Pregnancy test	3.5
	Virology	5
	CLL prognostic factors	5
	Total	**32**
Cycle 1, Day 1		
	Clinical chemistry	5
	Hematology	2.5
	Coagulation	3
	Anti-tislelizumab	2
	PK for zanubrutinib (2 samples @ 4 mL each)	8
	PK for tislelizumab (2 samples @ 5 mL each)	10
	Total	**30.5**
Other Cycles, Day 1 (± 3 days)		
	Clinical chemistry	5
	Hematology	2.5
	Coagulation	3
	IgA, IgG, and IgM level	5
	Thyroid function	3
	Total	**18.5**
Cycle 2, 5, 9, 17 Day 1 (± 3 days)		
	Clinical chemistry	5
	Hematology	2.5
	Coagulation	3
	IgA, IgG, and IgM level	5
	Thyroid function	3
	Anti-tislelizumab (Note: Cycle 5 has 2 samples @ 2 mL each)	2 (4 for Cycle 5)
	PK for zanubrutinib (Note: Cycle 5 has 2 samples @ 4 mL each)	4 (8 for Cycle 5)
	PK for tislelizumab (Note: Cycle 5 has 2 samples @ 5 mL each)	5 (10 for Cycle 5)
	Total	**29.5 (40.5 for Cycle 5)**
End of Cycles 2, 6, 12 (optional)[1]		
	For Cohort 4 subjects with CSF collection:	
	PK for zanubrutinib (Note: has 2 samples @ 4 mL each)	8
	PK for tislelizumab (Note: has 2 samples @ 5mL each)	10
	Total	**18**
Safety Follow-up		

Time point	Assessment	Total blood volume (mL)
	Clinical chemistry	5
	Hematology	2.5
	Coagulation	3
	IgA, IgG, and IgM level	5
	Thyroid function	3
	Anti-tislelizumab	2
	PK for tislelizumab	5
	Total	**25.5**
Efficacy Follow-up		
	Clinical chemistry	5
	Hematology	2.5
	IgA, IgG, and IgM level	5
	Total	**12.5**

CSF = cerebrospinal fluid; PK = pharmacokinetic

[1] CSF collection for drug measurements is optional for end of Cycles 2, 6, and 12.

APPENDIX 4: RESPONSE CRITERIA

Note: increases and decreases are relative to baseline unless otherwise indicated.

A) CHRONIC LYMPHOCYTIC LEUKEMIA

	Group A			**Group B**	**Bone Marrow‡**
Response*	**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	50% reduction in marrow infiltrate, or B-lymphoid nodules

				OR Hemoglobin > 11.0 g/dL or 50% improvement over baseline OR ANC > 1.5 x 10^9/L or > 50% improvement over baseline	
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.

B) NON-HODGKIN LYMPHOMA (including SLL)[21]

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

C) 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.

D) 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 Lugano criteria provided above for NHL response on PR status	50% decrease in enhancing tumor	Irrelevant	Minor RPE abnormality or normal	Negative
		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

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.

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).

c All CRs should be confirmed by repeat imaging; CR in the eyes should be confirmed by repeat evaluation.

d In the setting of primary leptomeningeal disease, PR is not recognized; all patients should be categorized as CR, CRu, SD, or PD.

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.

APPENDIX 5: DRUG DILUTION CALCULATION

Dose Level: 2 mg/kg

Body Weight (kg)	Total Administered Drug (mg)	Total Dose Volume (mL)	Drug Product Volume (mL)	Drug Product Volume (vial)	Aspirated 0.9% NaCl Volume (mL)	Target Final Concentration (mg/mL)
40	80	50	8.0	1	8.0	1.60
42	84	50	8.4	1	8.4	1.68
44	88	50	8.8	1	8.8	1.76
46	92	50	9.2	1	9.2	1.84
48	96	50	9.6	1	9.6	1.92
50	100	50	10.0	1	10.0	2.00
52	104	50	10.4	2	10.4	2.08
54	108	50	10.8	2	10.8	2.16
56	112	50	11.2	2	11.2	2.24
58	116	50	11.6	2	11.6	2.32
60	120	50	12.0	2	12.0	2.40
62	124	50	12.4	2	12.4	2.48
64	128	50	12.8	2	12.8	2.56
66	132	50	13.2	2	13.2	2.64
68	136	50	13.6	2	13.6	2.72
70	140	50	14.0	2	14.0	2.80
72	144	50	14.4	2	14.4	2.88
74	148	50	14.8	2	14.8	2.96
76	152	50	15.2	2	15.2	3.04
78	156	50	15.6	2	15.6	3.12
80	160	50	16.0	2	16.0	3.20
82	164	50	16.4	2	16.4	3.28
84	168	50	16.8	2	16.8	3.36
86	172	50	17.2	2	17.2	3.44
88	176	50	17.6	2	17.6	3.52
90	180	50	18.0	2	18.0	3.60
92	184	50	18.4	2	18.4	3.68
94	188	50	18.8	2	18.8	3.76
96	192	50	19.2	2	19.2	3.84
98	196	50	19.6	2	19.6	3.92
100	200	50	20.0	2	20.0	4.00

Dose Level: 5 mg/kg

Body Weight (kg)	Total Administered Drug (mg)	Total Dose Volume (mL)	Drug Product Volume (mL)	Drug Product Volume (vial)	Aspirated 0.9% NaCl Volume (mL)	Target Final Concentration (mg/mL)
40	200	100	20.0	2	20.0	2.00
42	210	100	21.0	3	21.0	2.10
44	220	100	22.0	3	22.0	2.20
46	230	100	23.0	3	23.0	2.30
48	240	100	24.0	3	24.0	2.40
50	250	100	25.0	3	25.0	2.50
52	260	100	26.0	3	26.0	2.60
54	270	100	27.0	3	27.0	2.70
56	280	100	28.0	3	28.0	2.80
58	290	100	29.0	3	29.0	2.90
60	300	100	30.0	3	30.0	3.00
62	310	100	31.0	4	31.0	3.10
64	320	100	32.0	4	32.0	3.20
66	330	100	33.0	4	33.0	3.30
68	340	100	34.0	4	34.0	3.40
70	350	100	35.0	4	35.0	3.50
72	360	100	36.0	4	36.0	3.60
74	370	100	37.0	4	37.0	3.70
76	380	100	38.0	4	38.0	3.80
78	390	100	39.0	4	39.0	3.90
80	400	100	40.0	4	40.0	4.00
82	410	100	41.0	5	41.0	4.10
84	420	100	42.0	5	42.0	4.20
86	430	100	43.0	5	43.0	4.30
88	440	100	44.0	5	44.0	4.40
90	450	100	45.0	5	45.0	4.50
92	460	100	46.0	5	46.0	4.60
94	470	100	47.0	5	47.0	4.70
96	480	100	48.0	5	48.0	4.80
98	490	100	49.0	5	49.0	4.90
100	500	100	50.0	5	50.0	5.00

APPENDIX 6: IMMUNE-RELATED ADVERSE EVENT EVALUATION AND MANAGEMENT

The recommendations below for the diagnosis and management of any irAE are intended as a guidance. This document should be used in conjunction with expert clinical judgement (by specialist physicians experienced in the treatment of cancer using immunological agents), and individual institutional guidelines or policies.

Criteria used to diagnose irAEs include blood tests, diagnostic imaging, histopathology, and microbiology assessments to exclude alternative causes such as infection, disease progression, and adverse effects of concomitant drugs. In addition to the results of these tests, the following factors should be considered when making an irAE diagnosis:

- What was the temporal relationship between initiation of tislelizumab and the adverse event?
- How did the patient respond to withdrawal of tislelizumab?
- Did the event recur when tislelizumab was reintroduced?
- Was there a clinical response to corticosteroids?
- Is the event an autoimmune endocrinopathy?
- Is disease progression or an alternative diagnosis a more likely explanation?
- When alternative explanations to autoimmune toxicity have been excluded, the irAE field associated with the AE in the eCRF should be checked.

Recommended Diagnostic Tests in the Management of Possible Immune-related AEs

Immune-related Toxicity	Diagnostic Evaluation Guideline
Thyroid Disorders	Scheduled and repeat thyroid function tests (TSH and T4).
Hypophysitis	Check visual fields and consider pituitary endocrine axis blood profile. Perform pituitary and whole brain MRI in patients with headache, visual disturbance, unexplained fatigue, asthenia, weight loss and unexplained constitutional symptoms. Consider consultation with an endocrinologist if an abnormality is detected.
Pneumonitis	All patients presenting with new or worsened pulmonary symptoms or signs, such as an upper respiratory infection, new cough, shortness of breath or hypoxia should be assessed by high-resolution CT. Consider pulmonary function test including DLCO. Radiographic appearance is often nonspecific. Depending on the location of the abnormality, bronchoscopy and bronchoalveolar lavage or lung biopsy may be considered. Consult with a respiratory medicine physician for cases of uncertain cause.
Neurological Toxicity	Perform a comprehensive neurological examination and brain MRI for all CNS symptoms; review alcohol history and other medications. Conduct a diabetic screen, and assess blood B12/folate, HIV status, TFTs, and consider autoimmune serology. Consider the need for brain/spine MRI/MRA and nerve conduction study for peripheral neuropathy. Consult with a neurologist if there are abnormal findings.
Colitis	Review dietary intake and exclude steatorrhea. Consider comprehensive testing, including the following: FBC, UEC, LFTs, CRP, TFTs, stool microscopy and culture, viral PCR, Clostridium difficile toxin, cryptosporidia (drug-resistant organism). In case of abdominal discomfort, consider imaging, eg, X-ray, CT scan. If a patient experiences bleeding, pain or distension, consider colonoscopy with biopsy and surgical intervention, as appropriate.
Eye Disorders	If a patient experiences acute, new onset, or worsening of eye inflammation, blurred vision, or other visual disturbances, refer the patient urgently to an ophthalmologist for evaluation and management.
Hepatitis	Check ALT/AST/total bilirubin, INR/albumin; the frequency will depend on severity of the AE (eg, daily if Grade 3-4; every 2-3 days if Grade 2, until recovering). Review medications (eg, statins, antibiotics) and alcohol history. Perform liver screen including Hepatitis A/B/C serology, Hepatitis E PCR and assess anti-ANA/SMA/LKM/SLA/LP/LCI, iron studies. Consider imaging, eg, ultrasound scan for metastases or thromboembolism. Consult with a hepatologist and consider liver biopsy.
Renal toxicity	Review hydration status and medication history. Test and culture urine. Consider renal ultrasound scan, protein assessment (dipstick/24-hour urine collection), or phase-contrast microscopy. Refer to nephrology for further management assistance.
Dermatology	Consider other causes by conducting a physical examination, consider dermatology referral for skin biopsy.
Rheumatology	Conduct musculoskeletal history and perform complete musculoskeletal examination. Consider joint X-ray and other imaging as required to exclude metastatic disease. Perform autoimmune serology and refer to rheumatology for further management assistance.
Joint or muscle inflammation	Conduct musculoskeletal history and perform complete musculoskeletal examination. Consider joint X-ray and other imaging as required to exclude metastatic disease. Perform autoimmune serology and refer to rheumatology for further management assistance. For suspected myositis/rhabdomyolysis/myasthenia include: CK, ESR, CRP, troponin and consider a muscle biopsy.
Myocarditis	Perform ECG, echocardiogram, troponin, and refer to a cardiologist.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; CNS, central nervous system; CRP, C-reactive protein; CT, computed tomography; DLCO, diffusing capacity for carbon monoxide; FBC, full blood count; HIV, human immunodeficiency virus; INR, international normalized ratio; LCI, liver cystolic antigen; LFT, liver function test; LKM, liver kidney microsomal antibody; LP, liver pancreas antigen; MRA, magnetic resonance angiogram; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; SLA, soluble liver antigen; SMA, smooth muscle antibody; T4, thyroxine; TFT, thyroid function tests; TSH, thyroid-stimulating hormone; UEC, urea electrolytes and creatinine

Treatment of Immune-Related Adverse Events

- Immune-related AEs can escalate quickly; study treatment interruption, close monitoring, timely diagnostic work-up and treatment intervention, as appropriate, with patients is required
- Immune-related AEs should improve promptly after introduction of immunosuppressive therapy. If this does not occur, review the diagnosis, seek further specialist advice and contact the study medical monitor
- For some Grade 3 toxicities that resolve quickly, rechallenge with study drug may be considered if there is evidence of a clinical response to study treatment, after consultation with the study medical monitor
- Steroid dosages in the table below are for oral or intravenous (methyl)prednisolone. Equivalent dosages of other corticosteroids can be substituted. For steroid-refractory irAEs, consider use of steroid-sparing agents (eg, mycophenolate mofetil [MMF])
- Consider prophylactic antibiotics for opportunistic infections if the patient is receiving long-term immunosuppressive therapy

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Thyroid Disorders	**1-2** Asymptomatic TFT abnormality or mild symptoms	Replace thyroxine if hypothyroid, until TSH/T4 levels return to normal range. Thyrotoxic patients should be referred to an endocrinologist. In cases with systemic symptoms: withhold study treatment, treat with a beta blocker and consider oral prednisolone 0.5 mg/kg/day for thyroid pain. Taper corticosteroids over 2-4 weeks. Monitor thyroid function regarding the need for hormone replacement.	Continue study treatment or withhold treatment in cases with systemic symptoms.
	3-4 Severe symptoms, hospitalization required	Refer patient to an endocrinologist. If hypothyroid, replace with thyroxine 0.5-1.6 µg/kg/day (for the elderly or those with co-morbidities,	Hold study treatment; resume when resolved/improved to grade 0-1.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
		the suggested starting dose is 0.5 µg/kg/day). Add oral prednisolone 0.5 mg/kg/day for thyroid pain. Thyrotoxic patients require treatment with a beta blocker and may require carbimazole until thyroiditis resolves.	
Hypophysitis	**1-2** Mild symptoms	Refer patient to an endocrinologist for hormone replacement. Add oral prednisolone 0.5-1 mg/kg/day for patients with pituitary inflammation. Taper corticosteroids over at least 1 month. If there is no improvement in 48 hours, treat as Grade 3-4. Taper corticosteroids over at least 1 month.	Continue study treatment.
	3-4 Moderate-severe symptoms	Refer patient to an endocrinologist for assessment and treatment. Initiate pulse IV methylprednisolone 1 mg/kg for patients with headache/visual disturbance due to pituitary inflammation. Convert to oral prednisolone and taper over at least 1 month. Maintain hormone replacement according to endocrinology advice. Maintain hormone replacement according to endocrinology advice.	Hold study treatment for patients with headache/visual disturbance due to pituitary inflammation until resolved/improved to Grade 2 or less. Discontinuation is usually not necessary.
Pneumonitis	**1** Radiographic changes only	Monitor symptoms every 2-3 days. If appearance worsens, treat as Grade 2.	Consider holding study treatment until appearance improves and cause is determined.
	2 Symptomatic: exertional breathlessness	Commence antibiotics if infection suspected. Add oral prednisolone 1 mg/kg/day if symptoms/appearance persist for 48 hours or worsen. Consider Pneumocystis infection prophylaxis. Taper corticosteroids over at least 6 weeks. Consider prophylaxis for adverse steroid effects: eg, blood glucose monitoring, vitamin D/calcium supplement.	Hold study treatment. Retreatment is acceptable if symptoms resolve completely or are controlled on prednisolone ≤ 10 mg/day. Discontinue study treatment if symptoms persist with corticosteroid treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3-4 Severe or life-threatening symptoms Breathless at rest	Admit to a hospital and initiate treatment with IV methylprednisolone 2-4 mg/kg/day. If there is no improvement, or worsening after 48 hours, add infliximab 5 mg/kg (if no hepatic involvement). Convert to oral prednisolone and taper over at least 2 months. Cover with empiric antibiotics and consider prophylaxis for Pneumocystis infection and other adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement.	Discontinue study treatment.
Neurological Toxicity	**1** Mild symptoms	–	Continue study treatment.
	2 Moderate symptoms	Treat with oral prednisolone 0.5-1 mg/kg/day. Taper over at least 4 weeks. Obtain neurology consultation.	Hold study treatment; resume when resolved/improved to Grade 0-1.
	3-4 Severe/life-threatening	Initiate treatment with oral prednisolone or IV methylprednisolone 1-2 mg/kg/day, depending on symptoms. Taper corticosteroids over at least 4 weeks. Consider azathioprine, MMF, cyclosporine if no response within 72-96 hours.	Discontinue study treatment.
Colitis/Diarrhea	**1** Mild symptoms: < 3 liquid stools per day over baseline and feeling well	Symptomatic management: fluids, loperamide, avoid high fiber/lactose diet. If Grade 1 persists for > 14 days manage as a Grade 2 event.	Continue study treatment.
	2 Moderate symptoms: 4-6 liquid stools per day over baseline, or abdominal pain, or blood in stool, or nausea, or nocturnal episodes	Oral prednisolone 0.5 mg/kg/day (non-enteric coated). Do not wait for any diagnostic tests to start treatment. Taper steroids over 2-4 weeks, consider endoscopy if symptoms are recurring.	Hold study treatment; resume when resolved/improved to baseline grade.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3 Severe symptoms: > 6 liquid stools per day over baseline, or if episodic within 1 hour of eating	Initiate IV methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Consider prophylaxis for adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement. If no improvement in 72 hours or symptoms worsen, consider infliximab 5 mg/kg if no perforation, sepsis, TB, hepatitis, NYHA grade III/IV CHF or other immunosuppressive treatment: MMF or tacrolimus. Consult gastroenterologist to conduct colonoscopy/ sigmoidoscopy.	Hold study treatment; retreatment may be considered when resolved/improved to baseline grade and after discussion with the study medical monitor.
	4 Life-threatening symptoms		Discontinue study treatment.
Skin reactions	**1** Skin rash, with or without symptoms, < 10% BSA	Avoid skin irritants and sun exposure; topical emollients recommended.	Continue study treatment.
	2 Rash covers 10%-30% of BSA	Avoid skin irritants and sun exposure; topical emollients recommended. Topical steroids (moderate strength cream once a day or potent cream twice a day) ± oral or topical antihistamines for itch. Consider a short course of oral steroids.	Continue study treatment.
	3 Rash covers > 30% BSA or Grade 2 with substantial symptoms	Avoid skin irritants and sun exposure; topical emollients recommended. Initiate steroids as follows based on clinical judgement: For moderate symptoms: oral prednisolone 0.5-1 mg/kg/day for 3 days then taper over 2-4 weeks. For severe symptoms: IV methylprednisolone 0.5-1 mg/kg/day; convert to oral prednisolone and taper over at least 4 weeks.	Hold study treatment. Re-treat when AE is resolved or improved to mild rash (Grade 1-2) after discussion with the study medical monitor.
	4 Skin sloughing > 30% BSA with associated symptoms (eg, erythema, purpura, epidermal detachment)	Initiate IV methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Admit to a hospital and seek urgent dermatology consultation.	Discontinue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Hepatitis	**1** ALT or AST > ULN to 3X ULN	Check LFTs within 1 week and before the next dose check LFTs to verify that there has been no worsening. If LFTs are worsening, recheck every 48-72 hours until improvement is seen.	Continue study treatment if LFTs are unchanged or improving. Hold study treatment if LFTs are worsening until improvement is seen.
	2 ALT or AST 3-5X ULN	Recheck LFTs every 48-72 hours: For persistent ALT/AST elevation: consider oral prednisolone 0.5-1 mg/kg/day for 3 days then taper over 2-4 weeks. For rising ALT/AST: start oral prednisolone 1 mg/kg/day and taper over 2-4 weeks; re-escalate dose if LFTs worsen, depending on clinical judgement.	Hold study treatment; treatment may be resumed when resolved/improved to baseline Grade and prednisolone tapered to ≤ 10 mg.
	3 ALT or AST 5-20X ULN	ALT/AST < 400 IU/L and normal bilirubin/INR/albumin: Initiate oral prednisolone 1 mg/kg and taper over at least 4 weeks. ALT/AST > 400 IU/L or raised bilirubin/INR/low albumin: Initiate IV (methyl)prednisolone 2 mg/kg/day. When LFTs improve to Grade 2 or lower, convert to oral prednisolone and taper over at least 4 weeks.	Hold study treatment until improved to baseline Grade; reintroduce only after discussion with the study medical monitor.
	4 ALT or AST > 20X ULN	Initiate IV methylprednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 6 weeks.	Discontinue study treatment.
	Worsening LFTs despite steroids: • If on oral prednisolone, change to pulsed IV methylprednisolone • If on IV, add mycophenolate mofetil (MMF) 500-1000 mg twice a day • If worsens on MMF, consider addition of tacrolimus Duration and dose of steroid required will depend on severity of event		
Nephritis	**1** Creatinine 1.5X baseline or > ULN to 1.5X ULN	Repeat creatinine weekly. If symptoms worsen, manage as per criteria below.	Continue study treatment.
	2 Creatinine > 1.5X-3X baseline or > 1.5X-3X ULN	Ensure hydration and review creatinine in 48-72 hours; if not improving, consider creatinine clearance measurement by 24-hour urine collection. Discuss with	Hold study treatment. If not attributed to drug toxicity, restart treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
		nephrologist the need for kidney biopsy. If attributed to study drug, initiate oral prednisolone 0.5-1 mg/kg and taper over at least 2 weeks. Repeat creatinine/U&E every 48-72 hours.	If attributed to study drug and resolved/improved to baseline grade: Restart study drug if tapered to < 10 mg prednisolone.
	3 Creatinine > 3X baseline or > 3X-6X ULN	Hospitalize patient for monitoring and fluid balance; repeat creatinine every 24 hours; refer to a nephrologist and discuss need for biopsy. If worsening, initiate IV (methyl)prednisolone 1-2 mg/kg. Taper corticosteroids over at least 4 weeks.	Hold study treatment until the cause is investigated. If study drug suspected: Discontinue study treatment.
	4 Creatinine > 6X ULN	As per Grade 3, patient should be managed in a hospital where renal replacement therapy is available.	Discontinue study treatment.
Diabetes/ Hyperglycemia	**1** Fasting glucose value ULN to 160 mg/dL; ULN to 8.9 mmol/L	Monitor closely and treat according to local guideline. Check for C-peptide and antibodies against glutamic acid decarboxylase and islet cells are recommended	Continue study treatment.
	2 Fasting glucose value 160-250 mg/dL; 8.9-13.9 mmol/L	Obtain a repeat blood glucose level at least every week. Manage according to local guideline.	Continue study treatment or hold treatment if hyperglycemia is worsening. Resume treatment when blood glucose is stabilized at baseline or Grade 0-1.
	3 Fasting glucose value 250-500 mg/dL; 13.9-27.8 mmol/L	Admit patient to hospital and refer to a diabetologist for hyperglycemia management. Corticosteroids may exacerbate hyperglycemia and should be avoided.	Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1.
	4 Fasting glucose value > 500 mg/dL; > 27.8 mmol/L	Admit patient to hospital and institute local emergency diabetes management. Refer the patient to a diabetologist for insulin maintenance and monitoring.	
Ocular Toxicity	**1** Asymptomatic eye exam/test abnormality	Consider alternative causes and prescribe topical treatment as required.	Continue study treatment.
	2 Anterior uveitis or mild	Refer patient to an ophthalmologist for assessment and topical corticosteroid treatment. Consider a	Continue study treatment or hold treatment if symptoms

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	symptoms	course of oral steroids.	worsen or if there are symptoms of visual disturbance.
	3 Posterior uveitis/ panuveitis or significant symptoms	Refer patient urgently to an ophthalmologist. Initiate oral prednisolone 1-2 mg/kg and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1; reintroduce only after discussion with the study medical monitor.
	4 Blindness (at least 20/200) in the affected eyes	Initiate IV (methyl)prednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks.	Discontinue study treatment.
Pancreatitis	**2** Asymptomatic, blood test abnormalities	Monitor pancreatic enzymes.	Continue study treatment.
	3 Abdominal pain, nausea and vomiting	Admit to hospital for urgent management. Initiate IV (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when amylase/lipase improved to Grade 2, and taper over at least 4 weeks.	Hold study treatment; reintroduce only after discussion with the study medical monitor.
	4 Acute abdominal pain, surgical emergency	Admit to hospital for emergency management and appropriate referral.	Discontinue study treatment.
Arthritis	**1** Mild pain with inflammation, swelling	Management per local guideline.	Continue study treatment.
	2 Moderate pain with inflammation, swelling, limited instrumental (fine motor) activities	Management as per local guideline. Consider referring patient to a rheumatologist. If symptoms worsen on treatment manage as a Grade 3 event.	Continue treatment or, if symptoms continue worsens, hold study treatment until symptoms improve to baseline or Grade 0-1.
	3 Severe pain with inflammation or permanent joint damage, daily living activity limited	Refer patient urgently to a rheumatologist for assessment and management. Initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks.	Hold study treatment unless improved to Grade 0-1; reintroduce only after discussion with the study medical monitor.
Mucositis/ stomatitis	**1** Test findings only or minimal symptoms	Consider topical treatment or analgesia as per local guideline.	Continue study treatment.
	2 Moderate pain, reduced	As per local guidelines, treat with analgesics, topical treatments and	Continue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	oral intake, limited instrumental activities	oral hygiene care. Ensure adequate hydration. If symptoms worsen or there is sepsis or bleeding, manage as a Grade 3 event.	
	3 Severe pain, limited food and fluid intake, daily living activity limited	Admit to hospital for appropriate management. Initiate IV (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when symptoms improved to Grade 2 and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1.
	4 Life-threatening complications or dehydration	Admit to hospital for emergency care. Consider IV corticosteroids if not contraindicated by infection.	Discontinue study treatment.
Myositis/ Rhabdomyolysis	**1** Mild weakness with/without pain	Prescribe analgesics. If CK is significantly elevated and patient has symptoms, consider oral steroids and treat as Grade 2	Continue study treatment.
	2 Moderate weakness with/without pain	If CK is 3 X ULN or worse initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks	Hold study treatment until improved to grade 0-1
	3-4 Severe weakness, limiting self-care	Admit to hospital and initiate oral prednisolone 1 mg/kg. Consider bolus IV (methyl)prednisolone and1-2 mg/kg/day maintenance for severe activity restriction or dysphagia. If symptoms do not improve add immunosuppressant therapy. Taper oral steroids over at least 4 weeks	Hold study treatment until improved to grade 0-1. Discontinue if any evidence of myocardial involvement
Myocarditis	**1** Asymptomatic but abnormal CK-MB, cardiac troponin or intraventricular conduction delay	Admit to hospital and refer to a cardiologist. Transfer all patients with moderate/severe cardiac symptoms or any increase in cardiac serum markers to the coronary care unit. Initiate oral prednisolone or IV (methyl)prednisolone at 1-2 mg/kg/day. Manage symptoms of cardiac failure according to local guidelines. If no immediate response change to pulsed doses of (methyl)prednisolone 1g/day and add MMF, infliximab or anti-thymocyte globulin	Hold study treatment until completely resolved or myocarditis has been ruled out.
	2 Symptoms on mild-moderate exertion		Discontinue study treatment unless cardiac involvement has been excluded and symptoms have completely resolved
	3 Severe symptoms with mild exertion		
	4 Life-threatening		

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; CHF, chronic heart failure; INR, international normalized ratio; IV, intravenous; LFT, liver function

test; MMF, mycophenolate mofetil; NYHA, New York Heart Association; T4, thyroxine; TB, tuberculosis; TFT, thyroid function test; TSH, thyroid-stimulating hormone; U&E, urea and electrolytes; ULN, upper limit of normal.