CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 1/2, Dose Escalation and Expansion Study of BGB-10188, a Phosphatidylinositol 3-Kinase Delta (PI3Kδ) Inhibitor, Combined With Zanubrutinib in Patients With Mature B-Cell Malignancies and Combined With Tislelizumab in Patients With Solid Tumors
Protocol Identifier:	BGB-A317-3111-10188-101
Phase:	1/2
Investigational Product(s):	BGB-10188, zanubrutinib (BGB-3111), tislelizumab (BGB-A317)
Indication:	Mature B-cell malignancies and advanced solid tumors
Sponsor:	BeiGene, Ltd. c/o BeiGene USA, Inc. 1840 Gateway Drive 3rd Floor San Mateo, CA 94404 USA BeiGene (Suzhou) Co., Ltd* Building 9, Biological Industrial Park No. 218 Sangtian Street Suzhou Industrial Park China (Jiangsu) Pilot Free Trade Zone Suzhou, Jiangsu, 215123, China * China sponsor for this study
Sponsor Medical Monitor	[redacted] Telephone: [redacted] Email: [redacted]
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FINAL PROTOCOL APPROVAL SHEET

A Phase 1/2, Dose Escalation and Expansion Study of BGB-10188, a Phosphatidylinositol 3-Kinase Delta (PI3Kδ) Inhibitor, Combined With Zanubrutinib in Patients With Mature B-Cell Malignancies and Combined With Tislelizumab in Patients With Solid Tumors

BeiGene, Ltd. Approval:

See electronic signature	*See electronic signature*
Sponsor Medical Monitor	Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES

The primary purposes of Amendment 7.0 are to reflect that Part C will not be initiated and that the higher doses of Part B will not enroll patients, and to add one condition for the end of study. The changes made in this amendment are described in the table below. Editorial and formatting changes are not included in this summary.

Protocol Amendment Summary of Changes Table

Section Number and Title	Summary of Change	Brief Rationale for Change
Section 2.1, Section 3.1, Section 3.3, Section 7.7, Section 9.8	Added or modified language to reflect that Part C (BGB-10188+ zanubrutinib dose expansion in patients with R/R FL, R/R MCL, R/R DLBCL) will not be initiated	Dose escalation of combination therapy (Part B) was suspended and no further development for combination therapy.
Section 5.5.1.1	Added safety management guidelines for diarrhea/colitis, rash, and pneumonitis to BGB-10188 in heme parts	Clarifying and improving safety management and monitoring regarding these potential safety risks.
Section 7.14	Added one condition for "the end of the study" for each part, which is at 12 months from C1D1 of the last enrolled patient in this part.	Clarifying wording regarding study closure.
Section 8.6.2.1, Section 8.6.2.2, Section 8.7.2	Added reporting requirements of adverse events of special interest (ie, diarrhea ≥ Grade 2 or Grade 1 lasting more than 7 days) for BGB-10188	Clarifying and improving safety management and monitoring regarding these potential safety risks.
Section 8.6.2	Updated the Reporting Method to Email or fax SAE form	More efficient reporting of SAEs.
Section 7.12.2, Appendix 1	Removed survival follow-up for patients in Part B	Maintaining consistency with study endpoints for Part B throughout the protocol.
Section 1.2.4, Section 1.5, and Section 8.1	Updated Prior Clinical Experience with BGB-10188, Benefit-Risk Assessment, and Risks Associated with Study Drug	Providing the most current available data.
Section 1.2, Section 8.1	Modified language on zanubrutinib and tislelizumab approval status	Providing the most current available information.
Section 8.6.5 and Section 8.6.6	Updated with clarified language for reporting disease progression and death on study	Providing clearer instructions for investigators.

Section Number and Title	Summary of Change	Brief Rationale for Change
Section 9.4.3	Modified language on PFS estimation in Part E	Clarifying planned analysis method
Section 10.1	Updated language on SMC meeting in Part E	Better reflecting study committee practices
Section 7.7, Section 7.8, Appendix 5	"First 5 patients in Part C and Part E, phospho-AKT expression in blood samples will be determined and used as a direct pharmacodynamic biomarker for PI3Kδ inhibition", changed to "*approximately* 5 patients…"	Correction of typographical errors

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SYNOPSIS

Name of Sponsor/Company: BeiGene, Ltd.
Investigational Products: BGB-10188, zanubrutinib (BGB-3111), and tislelizumab (BGB-A317)
Title of Study: A Phase 1/2, Dose Escalation and Expansion Study of BGB-10188, a Phosphatidylinositol 3-Kinase Delta (PI3Kδ) Inhibitor, Combined With Zanubrutinib in Patients With Mature B-Cell Malignancies and Combined With Tislelizumab in Patients With Solid Tumors
Protocol Identifier: BGB-A317-3111-10188-101
Phase of Development: 1/2
Number of Patients: Part A (n = 3 to 30, approximately) plus China verification part (n ≥ 3); Part B (n = 3 to 18, approximately); Part D (n = 3 to 30, approximately) plus China verification part (n ≥ 3); Part E (n = 30 to 50, approximately)
Study Centers: Approximately 35 in Australia and China (final site number may change)
Study Objectives: **Part A: BGB-10188 Monotherapy Dose Escalation in Patients With Relapsed/Refractory (R/R) Mature B-cell Malignancies** **Primary:** • To determine the maximum tolerated dose (MTD) and the recommended dose for expansion (RDFE) of BGB-10188 as monotherapy • To assess the safety and tolerability of BGB-10188 as monotherapy **Secondary:** • To evaluate the preliminary antitumor activity of BGB-10188 monotherapy as measured by investigator-assessed overall response rate • To characterize the pharmacokinetic profiles of BGB-10188 as monotherapy **Exploratory:** • To explore relationships between BGB-10188 concentrations and corrected QTcF intervals • To characterize the pharmacodynamic profiles of BGB-10188 after a single dose and at steady state • To explore the relationships between biomarkers and mechanisms of resistance and preliminary antitumor activity of BGB-10188 monotherapy

Part B: BGB-10188 + Zanubrutinib Dose Escalation in Patients With R/R Follicular Lymphoma, R/R Mantle Cell Lymphoma, or R/R Diffuse Large B-cell Lymphoma

Primary:

- To determine the MTD and the RDFE of BGB-10188 in combination with zanubrutinib
- To assess the safety and tolerability of BGB-10188 in combination with zanubrutinib

Secondary:

- To evaluate the preliminary antitumor activity of BGB-10188 in combination with zanubrutinib as measured by investigator-assessed overall response rate, duration of response (DOR), and time to response
- To characterize the pharmacokinetic profiles of BGB-10188 in combination with zanubrutinib

Exploratory:

- To characterize the pharmacokinetic profile of zanubrutinib when given in combination with BGB-10188
- To characterize the pharmacodynamic profiles of BGB-10188 in combination with zanubrutinib
- To explore the relationships between biomarkers and mechanisms of resistance and preliminary antitumor activity of BGB-10188 in combination with zanubrutinib

Part C: BGB-10188 + Zanubrutinib Dose Expansion in Patients With R/R Follicular Lymphoma, R/R Mantle Cell Lymphoma, or R/R Diffuse Large B-cell Lymphoma

Primary:

- To evaluate the preliminary antitumor activity of BGB-10188 in combination with zanubrutinib as measured by investigator-assessed overall response rate

Secondary:

- To evaluate the preliminary antitumor activity of BGB-10188 in combination with zanubrutinib as measured by investigator-assessed duration of response, time to response, and progression-free survival
- To assess the safety and tolerability of BGB-10188 in combination with zanubrutinib
- To characterize the pharmacokinetic profiles of BGB-10188 in combination with zanubrutinib

Exploratory:

- To evaluate the preliminary antitumor activity of BGB-10188 in combination with zanubrutinib as measured by overall survival
- To explore the relationships between biomarkers and mechanisms of resistance and preliminary antitumor activity of BGB-10188 in combination with zanubrutinib at RDFE
- To characterize the pharmacokinetic profile of zanubrutinib when given in combination with BGB-10188
- To characterize the pharmacodynamic profiles of BGB-10188 in combination with zanubrutinib at RDFE

Part D: BGB-10188 + Tislelizumab Dose Escalation in Patients With Advanced Solid Tumors

Primary:

- To determine the MTD and the RDFE of BGB-10188 in combination with tislelizumab
- To assess the safety and tolerability of BGB-10188 in combination with tislelizumab

Secondary:

- To evaluate the preliminary antitumor activity of BGB-10188 in combination with tislelizumab as measured by investigator-assessed overall response rate, duration of response, disease control rate, and time to response
- To characterize the pharmacokinetic profiles of BGB-10188 in combination with tislelizumab

Exploratory:

- To assess host immunogenicity to tislelizumab in combination with BGB-10188
- To characterize the pharmacodynamic profiles of BGB-10188 in combination with tislelizumab
- To explore the relationships between biomarkers and mechanisms of resistance and the preliminary anticancer activity of BGB-10188 in combination with tislelizumab

Part E: BGB-10188 + Tislelizumab Dose Expansion in Patients With Platinum-Resistant Ovarian Cancer (PROC)

Primary:

- To evaluate the preliminary antitumor activity of BGB-10188 in combination with tislelizumab in PROC as measured by the investigator-assessed overall response rate

- To assess the safety and tolerability of BGB-10188 in combination with tislelizumab

Secondary:

- To evaluate the preliminary antitumor activity of BGB-10188 in combination with tislelizumab as measured by investigator-assessed duration of response, progression-free survival, disease control rate, clinical benefit rate, and time to response
- To evaluate the preliminary antitumor activity of BGB-10188 in combination with tislelizumab as measured by locally assessed carcinoma antigen-125 (CA-125) response rate per Gynecological Cancer Intergroup for CA-125 changes
- To characterize the pharmacokinetic profiles of BGB-10188 in combination with tislelizumab

Exploratory:

- To assess host immunogenicity to tislelizumab in combination with BGB-10188
- To characterize the pharmacodynamic profiles of BGB-10188 in combination with tislelizumab at the recommended doses for expansion
- To explore the relationships between biomarkers and mechanisms of resistance and preliminary anticancer activity of BGB-10188 in combination with tislelizumab at the RDFE

Study Design:

This is an open-label, multicenter, dose escalation and dose expansion study to evaluate the safety and tolerability, determine the MTD and RDFE, and evaluate the preliminary antitumor activity of the following:

- BGB-10188 monotherapy in patients with mature B-cell malignancies, including R/R chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), R/R marginal zone lymphoma (MZL), R/R follicular lymphoma (FL), R/R mantle cell lymphoma (MCL), or R/R diffuse large B-cell lymphoma (DLBCL)
- BGB-10188 in combination with zanubrutinib in patients with R/R FL, R/R MCL, or R/R DLBCL
- BGB-10188 in combination with tislelizumab in patients with advanced solid tumors

The study consists of 5 parts, which are as follows:

- Part A, a dose escalation phase to determine the MTD/RDFE of BGB-10188 monotherapy in patients with R/R mature B-cell malignancies
- Part B, a dose escalation phase to determine the MTD/RDFE of BGB-10188 in combination with zanubrutinib in patients with R/R FL, R/R MCL, and R/R DLBCL

- Part C, a dose expansion phase for evaluation of BGB-10188 in combination with zanubrutinib at the RDFE in patients with R/R FL, R/R MCL, and R/R DLBCL. This Part was originally planned but was cancelled by the sponsor and will not be initiated.
- Part D, a dose escalation phase to determine the MTD/RDFE of BGB-10188 in combination with tislelizumab in patients with advanced solid tumors
- Part E, a dose expansion phase for evaluation of BGB-10188 in combination with tislelizumab at the RDFE in patients with platinum-resistant ovarian cancer (PROC)

The study design schematic is presented in Figure 1.

Part A is designed to test BGB-10188 monotherapy at 5 planned dose levels from 60 to 540 mg. Additional dose levels could be added per the Safety Monitoring Committee (SMC)'s recommendation based on safety, tolerability, and PK data. A Bayesian model-based dose escalation approach will be used for dose escalation and MTD determination of BGB-10188 monotherapy.

In Part B, approximately 3 dose levels will be tested to determine the MTD/RDFE of BGB-10188 in combination with zanubrutinib in patients with R/R FL, R/R MCL, and R/R DLBCL. The dose levels of BGB-10188 may be adjusted per SMC's recommendation according to the safety, tolerability and PK data. Additional dose levels could be added per the SMC's recommendation based on safety, tolerability, and PK data. The initial dose of BGB-10188 for Part B will be the latest cleared dose of BGB-10188 monotherapy in Part A. After the subsequent dose is identified to be safe in Part A, the same dose level in combination with zanubrutinib will be explored in Part B. A modified 3 + 3 design and dose escalation criteria will be used to determine the MTD for combination therapy of BGB-10188 and zanubrutinib.

When the dose of 120 mg once daily in Part A has been demonstrated safe, Part D, BGB-10188 dose escalation in combination with tislelizumab in patients with advanced solid tumors, will be triggered. In Part D, 6 planned dose levels of BGB-10188 will be tested with the initial dose of 20 mg once daily. The dose levels and dosages of BGB-10188 may be adjusted according to the safety and exposure results in Part A, and additional dose levels could be added if deemed appropriate. A Bayesian model-based-dose escalation approach will be used for dose escalation and MTD determination of the combination therapy with tislelizumab.

Dose expansion of BGB-10188 in combination with zanubrutinib (Part C) and BGB-10188 in combination with tislelizumab (Part E) will be explored after the RDFE of BGB-10188 in combination with zanubrutinib (Part B) or with tislelizumab (Part D) have been determined, respectively. In Part C, patients with R/R FL, R/R MCL, or R/R DLBCL will be enrolled. Part E is an open-label, randomized, multicenter, dose expansion phase to evaluate the safety and preliminary efficacy of BGB-10188 combined with tislelizumab in patients with PROC. Approximately 30 to 50 patients with PROC that have progressed on/after prior anticancer treatment and are CPI naïve will be randomized at a 2:1 ratio to receive either BGB-10188 (160 mg once daily) plus tislelizumab (200 mg once every 3 weeks) or BGB-10188 (320 mg once daily) plus tislelizumab (200 mg once every 3 weeks) until disease progression, intolerance, or patient withdrawal for other reasons.

In Part A, Part B, and Part C, a cycle is defined as 28 days in length. In Part D, a cycle is defined as 21 days in length except for Cycle 1, which is 28 days in length due to the dose-limiting toxicities (DLT) assessment period. In Part E, a cycle is defined as 21 days in length.

In Part A, Part B, and Part D, patients will be evaluated for DLT during Cycle 1. Patients will continue to be evaluated for DLTs up to 8 weeks due to late-onset toxicities that have been found to be associated with PI3Kδ inhibitors. A DLT is defined as an adverse event (AE) that meets one of the following criteria:

- Event occurs within 4 weeks (28 days) after start of study drug administration on C1D1, is related to the investigational agent, and is not due to alternative causes (eg, underlying disease, concurrent disease, or concomitant treatment):
  - Hematologic toxicity: Grade 4 neutropenia lasting > 7 days, ≥ Grade 3 febrile neutropenia, ≥ Grade 3 thrombocytopenia with ≥ Grade 2 bleeding, or Grade 4 thrombocytopenia lasting > 7 days
  - Nonhematologic toxicity: ≥ Grade 3 event persistent for > 7 days or any Grade of intracranial hemorrhage
  - Any toxicity that does not meet the abovementioned DLT criteria, but which leads to discontinuation or dosing interruption of > 7 days of BGB-10188 or zanubrutinib prior to Day 28, is considered a DLT.
- ≥ Grade 3 events of skin reaction, pneumonitis, colitis, diarrhea or increased alanine aminotransferase (ALT)/aspartate aminotransferase (AST) lasting > 7 days occur within a prolonged window up to 8 weeks (56 days) after starting BGB-10188 administration, is related to the investigational agent, and is not due to alternative causes (eg, underlying disease, concurrent disease, or concomitant treatment):

Note: For Part D only, the following AEs will not be considered DLTs: Grade 3 endocrinopathy that is adequately controlled by hormonal replacement, Grade 3 tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumors), or Grade 3 infusion-related AE that is transient (resolved within 6 hours of onset)

Study treatment will continue until disease progression, unacceptable toxicity, death, withdrawal of consent, lost to follow-up, end of study, investigator's decision, or the study is terminated by sponsor, whichever comes first.

Patients with disease progression in Part A can receive the cleared dose of BGB-10188 in combination with zanubrutinib at the investigator's discretion based on the local guidance and zanubrutinib prescribing information that the patients can benefit from treatment in combination with zanubrutinib. This should be discussed with and approved by the sponsor. The SMC will review the accumulated safety data and model result after the last patient (decided by the sponsor/SMC) or ≥ 3 DLT-evaluable patients of the current cohort, whichever occurs earlier, have completed the 28-day DLT observation period and make the recommendation on the dose level for the next cohort. Sponsor will make the final decision based on the recommendation of the SMC. The RDFE may not be the MTD since targeted therapies can achieve the desired antitumor effect at doses lower than the MTD.

Dose Verification in Chinese Patients (Part A and Part D)

Before enrollment of patients in China for Part B, Part C, and Part E of the study, the safety and tolerability of BGB-10188 as monotherapy (Part A) and in combination with tislelizumab (200 mg once every 3 weeks) (Part D) will be assessed in Chinese patients in accordance with detailed verification rules. For each cohort, approximately 3 to 6 Chinese patients will be enrolled to assess the safety and tolerability starting at the dose most recently identified as safe or the RDFE identified in Australian patients as outlined in Section 3.2.2. The DLT observation period will be 28 days, with a prolonged window of up to 8 weeks (ie, up to 56 days) for some specific events. After reviewing the accumulated safety data, including AEs and laboratory assessments, the SMC will recommend the RDFE for Chinese patients. The RDFE for Chinese patients will be determined based on the totality of the safety data and preliminary efficacy data of BGB-10188 as monotherapy and when combined with tislelizumab 200 mg before Chinese patients join Part B, Part C, and Part E.

Study Assessments:

Assessments of disease status during the study will include symptom-directed physical examination; disease-related constitutional symptoms (as necessary); complete blood count; bone marrow examination (as necessary); gastrointestinal examination (as necessary); and imaging scans.

Efficacy will be assessed by the investigators. For patients with chronic lymphocytic leukemia, disease response will be determined in accordance with the 2018 International Workshop on Chronic Lymphocytic Leukemia guidelines (Hallek et al 2018) with modification for treatment-related lymphocytosis (Cheson et al 2012). For patients with non-Hodgkin lymphoma (NHL) (including SLL, MCL, MZL, DLBCL, and FL), disease response will be determined in accordance with the Lugano Classification for non-Hodgkin lymphoma (Cheson et al 2014). For patients with advanced solid tumors, disease response will be determined per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) (Eisenhauer et al 2009).

Computed tomography (CT) scan with contrast of neck, chest, abdomen, and pelvis, plus any other disease sites will be performed at screening and, every 8 weeks for first 24 weeks, every

12 weeks for the next 24 weeks, and then every 16 weeks, and at End-of-Treatment (EOT) for Part A, Part B, and Part C. Patients in Parts A, B, and C with non-Hodgkin lymphoma (ie, MZL, MCL, FL, or DLBCL) will undergo positron emission tomography (PET)/CT imaging at baseline; a separate CT scan of diagnostic quality should be performed in addition to the PET/CT imaging if the PET/CT imaging is not of diagnostic quality. If PET-avid disease is detected, then subsequent tumor assessments should be conducted with PET/CT-based imaging. Patients in Parts A, B, and C with non-Hodgkin lymphoma without PET-avid disease, as well as patients with CLL/SLL, should undergo tumor assessments with CT-based imaging. 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, adheres to the specified slice thickness/scan parameters, and IV contrast is administered. Magnetic resonance imaging (MRI) may be substituted for patients with serious contrast allergy but should be used consistently. In Part D and Part E, tumor imaging will be performed at screening, Week 10 (Part D) or Week 9 (Part E), then every 9 weeks thereafter, and at EOT.

For patients who have mantle cell lymphoma with baseline gastrointestinal lymphoma involvement documented by endoscopic examination prior to first dose, a follow-up endoscopic examination will be performed at the time of suspected complete response to confirm complete response.

For patients who have bone marrow involvement of lymphoma by bone marrow biopsy at baseline, a bone marrow examination will be performed to confirm complete response. If a follow-up biopsy cannot be obtained, a PET scan that clearly documents continued disease clearance from bone marrow may be used in lieu of the repeated biopsy.

Assessments of safety will include AEs, serious adverse events, clinical laboratory tests, physical examinations, and vital signs. Adverse events will be graded for severity per the current version of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAT v5.0).

Blood samples for pharmacokinetics (PK) and pharmacodynamics analyses will be collected after single and repeat doses at specified timepoints in Parts A through Part E. In Part A only, all patients will receive a single dose of BGB-10188 followed by a washout period of 7 days.

For patients enrolled in Part A, Part B, or Part D, and approximately 5 patients in Part E, phospho-AKT expression in blood samples will be determined and used as a direct pharmacodynamic biomarker for PI3Kδ inhibition. Proportion and number of immune cells in blood samples will also be assessed to monitor pharmacodynamic changes by BGB-10188 treatment as monotherapy or in combination with zanubrutinib or tislelizumab.

Key Eligibility Criteria

For all parts of the study, eligible patients must be ≥ 18 years of age on the day of signing the informed consent form (or the legal age of consent in the jurisdiction in which the study is taking place); have an ECOG Performance Status of 0 or 1; and adequate organ function.

Part A, Part B, and Part C

Eligible patients must have a confirmed diagnosis of one of the following:

- Part A: R/R CLL/SLL, R/R MZL, R/R FL, R/R MCL, or R/R DLBCL
- Part B and Part C: R/R FL, R/R MCL, or R/R DLBCL

R/R disease is defined for patients who must have either: 1) disease progression after CR or PR of the last line of systemic therapy, or 2) failure to achieve CR or PR to the most recent appropriate systemic therapy.

Patients with SLL, FL, MZL, MCL, or DLBCL must have ≥ 1 bidimensionally measurable nodal lesion > 1.5 cm in the longest diameter or extranodal lesion that is > 1 cm in the longest diameter by CT scan or MRI, as defined by the Lugano Classification. Patients must have a life expectancy of > 4 months.

Patients should have no history of allogeneic stem-cell transplantation; prior exposure to PI3K inhibitor (or Bruton tyrosine kinase inhibitor for patients in Part B and Part C); no histologically confirmed transformed lymphoma; no clinically significant cardiovascular disease; no uncontrolled systemic infection requiring parenteral intravenous anti-infective therapy; and no active hepatitis B or C or HIV.

Part D and Part E

Eligible patients must have one of the following:

- Part D: Histologically or cytologically confirmed unresectable locally advanced or metastatic solid tumors previously treated with standard systemic therapy or for which effective standard treatment is not available or not tolerated. Patients must have ≥ 1 measurable lesion as defined by RECIST v1.1
- Part E: Histologically or cytologically confirmed epithelial ovarian cancer previously treated with 1 to 3 lines of systemic anticancer treatment and that is platinum-resistant and CPI naïve. Patients must have ≥ 1 measurable disease as assessed by RECIST v1.1.

Baseline tumor biopsy or available archived formalin-fixed paraffin-embedded (FFPE) tumor tissue sample (block or approximately 10 to 15 freshly cut unstained FFPE slides) is required. If a fresh tumor biopsy collected at screening is not available, archival samples are required.

Patients should have no prior exposure to PI3K inhibitor; no recent exposure to chemotherapy, immunotherapy (eg, interleukin, interferon, or thymosin), hormonal therapy, or any investigational agent or participation in another clinical study with therapeutic intent within 14 days or 5 half-lives (whichever is shorter) before first dose; no clinically uncontrolled pleural effusion, pericardial effusion, or ascites that requires drainage procedures within 14 days before first dose (Part D), or recurrence ≤ 14 days after intervention (Part E); no active leptomeningeal disease or uncontrolled brain metastasis; and no severe chronic or active infections, including active hepatitis B or C or HIV.

Test Product, Dose, and Mode of Administration

BGB-10188 will be administered orally, daily, in the morning on and with a glass of water (approximately 240 mL). In Part A, 5 proposed dose levels will be tested: 60 mg once daily, 120 mg once daily, 240 mg once daily, 360 mg once daily, and 540 mg once daily. The dose levels of BGB-10188 may be adjusted per SMC's recommendation according to the safety,

tolerability and PK data when combined with zanubrutinib. In Part B, approximately 3 dose levels will be tested: the latest cleared dose in Part A and the subsequent higher doses of Part A. In Part C, the RDFE determined in Part B will be tested. In Part D, 6 proposed dose levels will be tested: 20 mg once daily, 40 mg once daily, 80 mg once daily, 160 mg once daily, 320 mg once daily, and 540 mg once daily. In Part E, 2 proposed dose levels will be tested: 160 mg once daily and 320 mg once daily. Additional dose levels may be added if, based on emerging safety and tolerability data, exploration of additional doses (eg, 80 mg) is warranted and agreed by the SMC.

Zanubrutinib will be administered as two 80-mg capsules by mouth twice a day (160 mg twice daily) with or without food, with water at approximately the same time every day, with a minimum of 8 hours between consecutive doses. Zanubrutinib capsules should not be opened, broken, or chewed at any time.

Tislelizumab 200 mg will be administered on Day 8 of Cycle 1, and Day 1 of each subsequent cycle in Part D. In Part E, tislelizumab 200 mg will be administered on Day 1 of each cycle.

Statistical Methods

Analysis Sets:

Part A, Part B and Part C

- The DLT-Evaluable Set is defined as all patients who received ≥ 75% of the scheduled dose of each study treatment during the first 28-day treatment cycle. Additionally, patients who had a DLT event during the corresponding DLT observation window despite having received < 75% of the scheduled dose will also be considered evaluable.
- The Safety Analysis Set is defined as all patients who received ≥ 1 medication of BGB-10188 and/or zanubrutinib (for combination therapy part). This will be the primary analysis set used for safety analyses.
- The Efficacy Analysis Set is defined in the same way as the Safety Analysis Set and will be the primary analysis set used for efficacy analyses.
- The PK Analysis Set is defined as all patients who had ≥ 1 postdose plasma concentration and no important protocol deviation affecting PK.

Part D and Part E

- For Part D, the DLT-Evaluable Set is defined as all patients who received ≥ 75% of the scheduled dose of BGB-10188, ≥ 75% of the scheduled dose of tislelizumab during the first 28-day treatment cycle. Additionally, patients who had a DLT event during the corresponding DLT observation window despite having received < 75% of scheduled dose of tislelizumab or < 75% of the scheduled dose of BGB-10188 will also be considered evaluable.
- The Safety Analysis Set is defined as all patients who received at least one medication of BGB-10188 and/or tislelizumab. Patients are analyzed according to

the treatment they actually received. The Safety Analysis Set will be the primary analysis set used for safety analyses.

- The Efficacy Analysis Set is defined in the same way as the Safety Analysis Set in Part D. In Part E, the Efficacy Analysis Set follows the modified intent-to-treat principle and includes all patients who are randomized/enrolled and treated. The patients will be analyzed according to the treatment group to which they were randomized/enrolled to. The Efficacy Analysis Set will be the primary analysis set used for efficacy analyses.
- In Part E, the Efficacy Evaluable Analysis Set includes all patients who received at least one dose of study drugs, have evaluable disease at baseline, and have at least one evaluable postbaseline tumor response assessment unless any clinical disease progression or death occurred before the first postbaseline tumor assessment. The Efficacy Evaluable Analysis Set will be the sensitivity analysis set for efficacy analyses.
- The PK Analysis Set is defined as all patients who had at least one postdose plasma concentration and no major protocol deviation affecting PK.

Efficacy Analysis:

Efficacy analyses will be conducted by study part (where applicable) and indication based on the Efficacy Analysis Set. Overall response rate (ORR), disease control rate (DCR), clinical benefit rate, and CA-125 response rate will be summarized along with 95% CI using Clopper-Pearson method. Kaplan-Meier methodology will be used to estimate medians or other quartiles of duration of response (DOR) and progression-free survival (PFS), and their 95% CI will be constructed using Brookmeyer and Crowley method. Kaplan-Meier curves will also be provided. Time to response (TTR) will be summarized by descriptive statistics. DOR and TTR will be only analyzed for responders.

Safety Analysis:

Safety analyses will be conducted by study part, indication, dose level, and overall as appropriate based on the Safety Analysis Set. DLT events will be summarized by dose level for the dose escalation phase of each part. All treatment-emergent adverse events will be summarized. Serious adverse events, deaths, treatment-emergent adverse events ≥ Grade 3, immune-mediated adverse events (for Part D and Part E), treatment-related treatment-emergent adverse events, treatment-emergent adverse events that led to treatment discontinuation and/or dose modification, dose interruption, or dose delay will be summarized.

Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) for laboratory parameters and their changes from baseline will be calculated. Abnormal laboratory values will be flagged and identified as those outside (above or below) the normal range.

Descriptive statistics for vital sign parameters (eg, systolic and diastolic BP, heart rate, temperature) and changes from baseline will be presented by visit.

For Part D, ophthalmologic examination results will be listed by patient.

PK Analysis:

Blood samples will be collected to characterize the PK (and immunogenicity, if applicable) profiles of specified compounds. All blood sampling (plasma or serum) for PK assessment and antidrug antibody (ADA) testing (if applicable) will be collected at the timepoints specified in the Schedule of Assessments. The actual collection date and time of each blood sample will be recorded. The timing of PK and ADA samples may be altered and/or PK and ADA samples may be obtained at additional timepoints upon sponsor approval to ensure thorough PK and ADA monitoring.

Sample Size:

For Part A, Part B, and Part D, the number of dose levels examined, the dose escalation cohort size, and the emerging toxicities of the therapy will determine the sample size. Patients will be recruited with a targeted cohort size of 3, although flexibility in cohort size is allowed with the model-based dose escalation as well as for a modified 3 + 3 design.

Approximately 5 dose levels are planned for the dose escalation path of BGB-10188 monotherapy in Part A. A total of approximately 30 patients are expected to be enrolled for the BGB-10188 monotherapy dose escalation. The dose levels of BGB-10188 for the combination therapy in Part B with zanubrutinib 160 mg twice daily will be the latest cleared dose and subsequent higher dose levels from the monotherapy dose escalation. Therefore, a total of approximately 18 patients are expected to be enrolled for the combination therapy dose escalation.

Approximately 6 dose levels of BGB-10188 are planned for the combination therapy dose escalation with tislelizumab 200 mg once every 3 weeks in Part D. A total of approximately 36 patients are expected to be enrolled.

The total sample size in Part A, Part B, and Part D is expected to be approximately 84, excluding patients for the China verification parts. Part E is expected to have approximately 30 to 50 patients. Part C was designed to have approximately 20 patients but will not be initiated. The sample size for China verification parts will be based on the escalation status in Part A and Part D.

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
ALT	alanine aminotransferase
ADA	antidrug antibody
AE	adverse event
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the concentration curve
BGB-3111	zanubrutinib
BGB-A317	tislelizumab
BLRM	Bayesian logistic regression model
BPH	Bayesian proportional hazard
BTK	Bruton tyrosine kinase
CBC	complete blood count
CD	cluster of differentiation
CL	clearance
CLL	chronic lymphocytic leukemia
CMV	cytomegalovirus
CNS	central nervous system
CPI	checkpoint inhibitor
CR	complete response
CT	computed tomography
CTLA-4	cytotoxic T lymphocyte-associated antigen-4
CYP	cytochrome P450
DCR	disease control rate
DLBCL	diffuse large B-cell lymphoma
DLCO	carbon monoxide diffusion capacity
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
eCRF	electronic case report form
EOT	End-of-Treatment (Visit)
FDA	Food and Drug Administration

Abbreviation	Definition
FFPE	formalin-fixed paraffin-embedded
FEV1	forced expiratory volume in 1 second
FL	follicular lymphoma
FVC	forced vital capacity
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBcAb	hepatitis B core antibody
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
imAE	immune-mediated adverse event
IRB	Institutional Review Board
IRR	infusion-related reaction
iwCLL	International Workshop on CLL
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MZL	marginal zone lymphoma
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin lymphoma
NMPA	National Medical Products Administration
NOAEL	no observed adverse effect level
NSCLC	non-small cell lung cancer
OC	ovarian cancer
ORR	overall response rate
OS	overall survival
P-gp	P-glycoprotein

Abbreviation	Definition
PD-1	programmed cell death protein-1
PD-L1	programmed cell death protein ligand-1
PET	positron emission tomography
PFS	progression-free survival
PI3Kδ	phosphatidylinositol 3-kinase delta
PJP	pneumocystis jirovecii pneumonia
PK	pharmacokinetic(s)
PR	partial response
PROC	platinum-resistant ovarian cancer
PT	preferred term
RDFE	recommended dose for expansion
RECIST	Response Evaluation Criteria in Solid Tumors
R/R	relapsed/refractory
SAE	serious adverse event
SLL	small lymphocytic lymphoma
SMC	Safety Monitoring Committee
SOC	system organ class
TEAE	treatment-emergent adverse event
TGI	tumor growth inhibition
Treg	T-regulatory (cell)
TTR	time to response
ULN	upper limit of normal
US	United States
WM	Waldenström macroglobulinemia

1. INTRODUCTION AND RATIONALE

1.1. Background on Phosphatidylinositol 3-Kinase δ

Phosphatidylinositol 3-kinase δ (PI3Kδ) is frequently active in B-cell malignancies and is central to multiple signaling pathways that drive proliferation, survival, homing, and retention of malignant B-cells in lymphoid tissue and bone marrow. In B-cell malignancies, PI3K pathway activity is significantly elevated, which is driven by altered B-cell receptor signaling together with other co-stimulatory signals present in lymphoid tissues such as chemokines and cytokines (Puri and Gold 2012; Okkenhaug and Vanhaesebroeck 2003). PI3Kδ functions to integrate and transduce these signals from the microenvironment, thus promoting malignant B-cell proliferation, growth, survival, adhesion, and homing, making it an attractive drug target for B-cell malignancies (Yang et al 2015).

PI3Kδ is also important for the homeostasis and function of T-regulatory (Treg) cells (Lim and Okkenhaug 2019). The inactivation of PI3Kδ in mice can stimulate immune responses against solid tumors via the inhibition of Treg cells (Ali et al 2014). With PI3Kδ expression at low or undetectable levels in most organs, inhibitors against PI3Kδ should be selective for the immune system and less toxic (Okkenhaug and Fruman 2010).

Because of the specific and critical functions of PI3Kδ in adaptive immune responses, inhibitors of PI3Kδ are being developed for the treatment of autoimmune and inflammatory disorders, hematologic and solid tumors, and activated PI3Kδ syndrome (Lucas et al 2016; Okkenhaug and Burger 2016). PI3Kδ inhibitors are also being developed for the treatment of solid tumors because PI3Kδ is essential for the homeostasis and function of Foxp3+ Treg cells (Patton et al 2006). Loss of PI3Kδ activity, especially by specific deletion in Treg cells, can restrict the growth of transplanted tumors in mice (Ali et al 2014), providing a rationale for the evaluation of PI3Kδ inhibitors in solid tumors.

Since 2014, PI3Kδ inhibitors have been approved for treatment against B-cell malignancies. Zydelig® (idelalisib), the first PI3Kδ inhibitor approved in the USA, is indicated in combination with rituximab for the treatment of adult patients with relapsed chronic lymphocytic leukemia (CLL) (Brown et al 2014; Furman et al 2014; Zydelig® 2022). Response rates for CLL in a Phase 1 trial evaluating several dose levels (50 to 350 mg once or twice daily) were reported as 72% (95% CI: 58.4% to 83.5%) (39/54), with 39% (21/54) of patients meeting the criteria for partial response (PR) per International Workshop on CLL (iwCLL) 2008 criteria and 33% (18/54) meeting the criteria of PR in the presence of treatment-induced lymphocytosis (Brown et al 2014).

Copanlisib was approved by the United States (US) Food and Drug Administration (FDA) in 2017 for the treatment of adult patients with relapsed follicular lymphoma (FL) who have received ≥ 2 prior systemic therapies, and granted conditional approval by the China National Medical Products Administration (NMPA) in May 2023 for the treatment of patients with relapsed/refractory (R/R) FL after ≥ 2 prior therapies. It was granted breakthrough therapy designation by the FDA for relapsed marginal zone lymphoma (MZL) with ≥ 2 prior therapies based on data from the Phase 2 CHRONOS-1 study. In the FL subset, the overall response rate (ORR) was 58.7%, including 14.4% complete response (CR) and 44.2% PR. In the MZL subset, the ORR was 69.6%, including 8.7% CR and 60.9% PR. The estimated Kaplan-Meier median

duration of response (DOR) in the full analysis set was 687 days (range: 0 to 687 days) and 370 days (range: 0 to 687 days) in the FL subset. The Kaplan-Meier estimate of median progression-free survival (PFS) was 340 days (range: 0 to 736 days). The median overall survival (OS) had not yet been reached (Dreyling et al 2017).

Duvelisib was approved by the US FDA in 2018 for the treatment of R/R CLL or small lymphocytic lymphoma (SLL) after ≥ 2 prior therapies, and approved by the China NMPA in March 2022 for the treatment of patients with R/R FL after ≥ 2 prior therapies. The CLL and SLL indication is based on a randomized, multicenter, open-label trial (NCT02004522) comparing duvelisib to ofatumumab in patients with R/R CLL or SLL the estimated median PFS, as assessed by an Independent Review Committee (IRC), was 16.4 months in the duvelisib arm and 9.1 months in the ofatumumab arm (hazard ratio of 0.40; standard error 0.2). The ORR per IRC was 78% and 39% for the duvelisib and ofatumumab arms, respectively (39% difference, standard error 6.5%) (Flinn et al 2018). Duvelisib results in an ORR of 83% per the IRC for Chinese patients with R/R FL. Median DOR, PFS, and OS have not been reached. Median time to response (TTR) was 1.8 (range: 1.6 to 5.5) months by the IRC. Treatment-related adverse events (TRAEs) of any grade occurred in 21 (91%) of 23 patients, in which 12 (52%) were ≥ Grade 3 (Zheng et al 2021).

Linperlisib was granted conditional approval by the China NMPA for adult patients with R/R FL who have failed at least two prior systemic therapies in November 2022 based on the Phase 2 YY-20394 study (NCT04370405). The results of the study indicated an ORR of 80.9% and a disease control rate (DCR) of 96.6% in 89 evaluable patients with R/R FL (Yingli Pharma 2021).

Parsaclisib was granted breakthrough therapy designation by the China NMPA for R/R FL in March 2021 based on the Phase 2 study (CTR20192392). Parsaclisib demonstrated an ORR of 69.8% and a CR of 13.5% in 96 evaluable patients with R/R FL (Lynch et al 2020).

TQ-B3525, a novel and selective oral PI3K α/δ inhibitor, was granted breakthrough therapy designation by the China NMPA for R/R FL in July 2021 based on the Phase 1 study (NCT03510767). The results of the study indicated an ORR of 72.7% in 11 evaluable patients with R/R FL, and the longest DOR of 11.8 months at data cutoff in a patient with FL (Wang et al 2020).

Although the approved agents have impressive clinical activity in CLL/SLL, MZL, and FL, some are associated with substantial toxicity. In particular, fatal or life-threatening hepatotoxicity, colitis, and pneumonitis for idelalisib and fatal or serious infection, colitis, cutaneous reactions, and pneumonitis for duvelisib. A PI3Kδ inhibitor with an improved therapeutic index would represent an important advance for these patients.

1.2. Background Information on BGB-10188 (PI3Kδ Inhibitor), Zanubrutinib (BTK Inhibitor), and Tislelizumab (PD-1 Antibody)

BGB-10188

BGB-10188 is a potent, selective, orally active inhibitor of PI3Kδ with more than 3000-fold selectivity against other Class I PI3K isoforms and no inhibitory effect on 17 lipid kinases, 376 protein kinases, and 87 non-kinase enzymes, including G-protein-coupled receptors, transporters, ion channels, and nuclear receptors. BGB-10188 is about 10- to 20-fold more

potent than idelalisib in whole blood assays with an IC_{50} of 9.2 nM versus 189 nM. BGB-10188 has low permeability, but its solubility is high. It has no effect on cytochrome P450 (CYP) inhibition or induction, it is a P-glycoprotein (P-gp) substrate and does not penetrate the blood-brain-barrier. The results of nonclinical efficacy studies suggest that BGB-10188 (BGB-10188 Investigator's Brochure [IB]) as monotherapy or in combination with the Bruton tyrosine kinase (BTK) inhibitors could significantly inhibit the growth of B-cell malignancies. In Farage diffuse large B-cell lymphoma (DLBCL) and JeKo-1 mantle cell lymphoma (MCL) xenograft models, BGB-10188, as a single agent, showed significant antitumor activities with tumor growth inhibition (TGI) of 22% to 62% at doses ranging from 10 to 100 mg/kg. In combination with BGB-3111 (2.5 mg/kg) in TMD-8 DLBCL model, BGB-10188 treatment increased the TGI from 77% to 101% (versus 68% for BGB-3111 alone) on treatment Day 14, and tumor shrinkage was observed in all combination treatment groups after treatment for 20 days. In combination with BGB-3111 (7.5 mg/kg) in Jeko-1 MCL model, the TGI in combination treatment groups was increased from 75% to 84% (versus 43% for BGB-3111 alone) at doses of 10 to 30 mg/kg for BGB-10188. BGB-10188 could also inhibit the growth of solid tumors in combination with the programmed cell death protein-1 (PD-1) antibodies. In the CT26WT mouse colon cancer syngeneic model, BGB-10188 combined with anti-mouse PD-1 antibody muCh15mt significantly increased the TGI and tumor free animal percentage (TF%) compared with single agent alone at doses of 10 to 30 mg/kg (TGI increased to 72% to 88% versus 21% to 56% in single agent groups; TF% increased to 54% to 71% versus 0 to 37% in single agent groups). In Good Laboratory Practice (GLP) toxicity studies, BGB-10188 had greater safety margins than idelalisib and the PI3Kα,δ inhibitor copanlisib, which was approved for the treatment of B-cell malignancies in 2017 (Krause et al 2018).

BGB-10188 is a novel PI3Kδ inhibitor with high selectivity and a safety profile that in nonclinical studies is improved over the safety of approved inhibitors of PI3K enzymes. These characteristics of BGB-10188 are encouraging and warrant its testing in humans.

Zanubrutinib

Zanubrutinib (also known as BGB-3111) is a novel, irreversible, second-generation BTK inhibitor with great potency and selectivity. In both biochemical and cellular assays, zanubrutinib has demonstrated potent BTK inhibition activity. Zanubrutinib is more selective than ibrutinib (an approved BTK inhibitor) against off-target kinases, including *EGFR*, *JAK3*, *HER2*, *TEC*, *ITK*, and others. Zanubrutinib has also demonstrated better antitumor activity than ibrutinib in human MCL and DLBCL xenograft models. Unlike ibrutinib, zanubrutinib has not been shown to interfere with the anti-cluster of differentiation (CD)20 antibody-induced antibody-dependent cellular cytotoxicity effect. Zanubrutinib has received approvals for the indications of MCL, WM, MZL, CLL/SLL, and FL in over 65 countries/regions worldwide (including all EU states).

Tislelizumab

Tislelizumab (also known as BGB-A317) is a humanized immunoglobulin G4 variant monoclonal antibody against the immune checkpoint-inhibitory receptor, PD-1. Tislelizumab binds to the extracellular domain of human PD-1 with high specificity and affinity. Also, with an edited gamma fragment crystallizable region receptor IIIA, tislelizumab had low or no antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity effects in

humans (Labrijn et al 2009). Tislelizumab has been approved in China, Macao China, US, Europe, and South Korea. In China and Macao China, it has been approved as monotherapy or in combination with chemotherapy, for the treatment of patients with R/R classical Hodgkin lymphoma, locally advanced or metastatic urothelial carcinoma, locally advanced or metastatic squamous non-small cell lung cancer (NSCLC), locally advanced or metastatic nonsquamous NSCLC, previously treated hepatocellular carcinoma, advanced unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, previously treated locally advanced or metastatic esophageal squamous cell carcinoma (ESCC), and metastatic nasopharyngeal cancer. In China, it has also been approved as the first line treatment with chemotherapy in locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma with high PD-L1 expression; first line treatment in locally advanced, recurrent, or metastatic ESCC; and as monotherapy in first line treatment of unresectable or metastatic HCC. In US, Europe, and South Korea, tislelizumab has been approved for treatment in previously treated ESCC.

1.2.1. Pharmacology

BGB-10188

BGB-10188 is a potent and selective inhibitor of PI3Kδ in biochemical and cellular assays. BGB-10188 inhibited cellular growth of several DLBCL and MCL cell lines in vitro.

In vivo studies showed that BGB-10188 induced dose-dependent antitumor effects against Farage DLBCL xenografts engrafted either subcutaneously or systemically in mice. In addition, BGB-10188 showed combination therapeutic effects with a BTK inhibitor (zanubrutinib) in Farage and TMD8 DLBCL, as well as JEKO-1 and MINO MCL subcutaneous xenografts at doses of 10 to 30 mg/kg. In the CT26WT syngeneic mouse colon tumor model, BGB-10188 showed combination inhibitory effects with anti-mouse PD-1 antibody on tumor growth at doses from 3 to 30 mg/kg in a dose-dependent manner.

Zanubrutinib

Zanubrutinib has been administered to approximately 2772 patients. Refer to Section 1.2.3 for the clinical pharmacology data.

Tislelizumab

Tislelizumab has been administered to 3220 patients (as a monotherapy or in combination with chemotherapy), refer to Section 1.2.3 for the clinical pharmacology data.

1.2.2. Toxicology

BGB-10188

In the 28-day repeat dose study in rats, mortalities were only noted in 7/15 females at the high dose of 500 mg/kg/day with similar changes and more severity as compared to the surviving animals in this group. At the dose of 500 mg/kg/day, adverse histopathological changes were noted in the liver, brain, heart, non-glandular stomach, esophagus, thymus and mesenteric lymph node, skeletal muscle, and female reproductive organs, which were mainly characterized by hypertrophy/atrophy/hyperplasia, degeneration/necrosis/cell loss, mixed cell infiltration, decreased lymphocytes, and/or vacuolation and correlated with clinical pathology changes.

Non-adverse changes in other multiple tissues and/or organs were mainly characterized by hypertrophy, vacuolation, and macrophage aggregation/vacuolation/infiltration, apoptosis, neutrophilic inflammation, increased myeloid cellularity, decreased lymphocytes. At the dose of 150 mg/kg/day, adverse changes in the liver were characterized by mild hypertrophy/hyperplasia in the biliary. No test article-related changes were noted in animals at the dose of 50 mg/kg/day except for lymphoid depletion, increased tingible body macrophages in peripheral lymphoid tissues, vacuolated macrophage infiltration in the testes, and minimal changes in the liver, which were not considered adverse. All above changes were reversible. The maximum tolerated dose (MTD) was considered to be 150 mg/kg/day, and the no observed adverse effect level (NOAEL) was considered to be 50 mg/kg/day.

While dogs were orally administered BGB-10188 at single doses up to 300 mg/kg, or at 28-day repeated doses up to 60 mg/kg/day, no mortality was noted. Dose-dependent hypersensitive-like clinical signs or changes, including red skin discoloration, swelling, salivation, decreased activity, vomitus, increased respiratory rate, prostration, tremors, and/or increased heart rate and decreased BP were noted in dogs after dosing from 30 to 300 mg/kg/day. Those findings/changes were not noted at the dose of 10 mg/kg/day. The histopathological changes were noted in liver, gallbladder, heart, bone marrow, and lymphoid tissues that were correlated with decreases in body weights; increases in white blood cells (WBCs) and/or its differential (monocytes, lymphocytes, neutrophils), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase, and total bilirubin; and decrease in reticulocytes. All changes were reversible, and only changes in liver and gallbladder at the dose of 60 mg/kg/day were considered adverse. Based on the results, the MTD was considered to be 60 mg/kg/day; the NOAEL was considered to be 30 mg/kg/day.

The systemic exposure increased dose proportionally in rats with 1.7- to 2.7-fold higher exposure in females than males, while it increased more than dose proportionally in dogs and without marked sex difference. Slight accumulation (area under the concentration curve [AUC] indices: 1.1 to 3.5) was indicated after repeated doses in both rats and dogs.

Based on genotoxicity core battery studies, BGB-10188 is considered lack of genotoxic potential and low concern for human safety (International Council for Harmonisation [ICH] S2[R1]).

The phototoxic potential is considered based on the photochemical properties with molar extinction coefficient greater than 1000 $L \cdot mol^{-1} \cdot cm^{-1}$ between 290 and 347 nm.

In summary, the toxicity and toxicokinetic profiles of BGB-10188 were well characterized in both rats and dogs. Based on ICH S9, all the available toxicology studies and data are considered adequate to support the first in patient dosing and the clinical development of BGB-10188 for treatment of patients with advanced cancer.

Zanubrutinib

Zanubrutinib has been administered to approximately 2772 patients as of the data cutoff date of 30 November 2022. Refer to Section 1.2.4 for prior clinical experience information. Please refer to the zanubrutinib IB for more detailed information on the toxicology of zanubrutinib.

Tislelizumab

Tislelizumab has been administered to 2377 patients as a monotherapy and 2019 in combination with chemotherapy as of the data cutoff date of 27 October 2023. Refer to Section 1.2.4 for prior

clinical experience information. Please refer to the tislelizumab IB for more detailed information on the toxicology of tislelizumab.

1.2.3. Clinical Pharmacology

BGB-10188

The pharmacokinetics (PK) of BGB-10188 is being studied in this first-in-human study BGB-A317-3111-10188-101, which consists of 5 Parts (A to E). As of 06 March 2023, preliminary PK parameters showed that BGB-10188 was rapidly absorbed with T_{max} of approximately 2 hours. The PK of BGB-10188 was characterized with a fast distribution phase followed by an elimination phase with mean terminal half-life ranging from 8 to 31 hours across the cohorts. The dose normalized observed maximum plasma concentration (C_{max}) and $AUC_{0\text{-}24h}$ of BGB-10188 are comparable between monotherapy in Part A and in combination therapy with tislelizumab (Part D), indicating tislelizumab had no significant impact on BGB-10188 PK.

Little or low accumulation of BGB-10188 plasma AUC was observed after repeated dosing once daily compared to that after a single dose. BGB-10188 exposure increased with each dose level in more than a dose-proportional manner both after the single dose and at steady state when the dose increased to 240 mg.

For more detailed information on the clinical pharmacology of BGB-10188, refer to the IB (BGB-10188 IB).

Zanubrutinib

Zanubrutinib is rapidly absorbed and eliminated after oral administration in human subjects. The mean elimination half-life ($t_{½}$) was between 2 and 4 hours, and peak concentrations occurred around 2 hours postdose. The C_{max} and AUC increased in a nearly dose-proportional manner from 40 to 320 mg, after single-dose or repeated-dose administrations. Zanubrutinib was primarily eliminated by hepatic metabolism and fecal excretion. The food-effect study showed that the increase in C_{max} (51%) and $AUC_{0\text{-}inf}$ (12%) observed when zanubrutinib was given with a low-fat meal compared to the fasted state are not considered to be clinically relevant; therefore, zanubrutinib can be administered with or without food.

Single oral doses of zanubrutinib at 160 and 480 mg did not have a clinically relevant effect on electrocardiogram (ECG) parameters, including QTc intervals and other ECG intervals.

Clinical drug-drug interaction study showed that the dose of zanubrutinib needs to be modified when coadministered with moderate or strong CYP3A inhibitors, and to be avoided when coadministered with moderate or strong CYP3A inducers (refer to Zanubrutinib Prescribing Information 2019).

A dedicated hepatic impairment study (BGB-3111-107) showed that there was no substantial difference in PK profiles between patients with mild/moderate hepatic impairment and healthy subjects.

Dosage modification of zanubrutinib is recommended in patients with severe hepatic impairment. No dosage modification is recommended in patients with mild to moderate renal impairment.

For more detailed information on the clinical pharmacology experience for zanubrutinib, please refer to the IB (zanubrutinib IB).

Tislelizumab

A population PK analysis was performed based on pooled data (PK, dosing information, demographics, and patient or disease characteristics) from 2596 patients across 12 clinical studies (BGB-A317_Study_001, BGB-A317-102, BGB-A317-203, BGB-A317-204, BGB-A317-205, BGB-A317-206, BGB-A317-208, BGB-A317-209, BGB-A317-302, BGB-A317-303, BGB-A317-304, and BGB-A317-307). The PK of tislelizumab was best characterized using a 3-compartmental linear population PK model with linear clearance mechanisms. No time-varying clearance was observed in tislelizumab PK. The typical estimates of clearance (CL), central volume of distribution (V_c), and peripheral volumes 2 and 3 (V_2 and V_3, respectively), were 0.153 L/day, 3.05 L, 1.27 L, and 2.10 L, respectively, with interindividual variability in CL (26.3%), V_c (16.7%), V_2 (74.7%), and V_3 (99.9%). The terminal $t_{½}$ was estimated to be approximately 23.8 days.

The population PK analyses demonstrated that race, baseline ALT, AST, bilirubin, lactate dehydrogenase, estimated glomerular filtration rate (eGFR), ECOG Performance Status score, and sum of products of perpendicular diameters of classical Hodgkin lymphoma did not have statistically significant influences on tislelizumab PK. Baseline body weight, tumor size of solid tumors, albumin, age, sex, immunogenicity, and tumor type were found to be statistically significant covariates on the PK of tislelizumab; however, the exposure changes by these covariates were small compared to the overall estimated PK exposures range and hence are not considered clinically meaningful.

For more detailed information on the clinical pharmacology experience for tislelizumab, please refer to the IB (tislelizumab IB).

1.2.4. Prior Clinical Experience

1.2.4.1. BGB-10188

BGB-10188 is being studied in this 1 ongoing clinical trial in Australia and China. For details on the clinical efficacy of BGB-10188, refer to the BGB-10188 Investigator's Brochure.

1.2.4.2. Zanubrutinib

For details on the clinical efficacy of zanubrutinib, refer to the zanubrutinib Prescribing Information (Brukinsa [zanubrutinib] US prescribing information 2019).

1.2.4.3. Tislelizumab

For details on the clinical efficacy of tislelizumab, refer to the tislelizumab Prescribing Information (Tevimbra [tislelizumab] US prescribing information 2024).

1.3. Study Rationale

1.3.1. Rationale for Combination of BGB-10188 and Zanubrutinib in the Treatment of B-Cell Malignancies

PI3Kδ and BTK are downstream intermediaries of B-cell receptor signaling and are essential for B-cell activation, proliferation, and survival. Both have unique roles in B-cell receptor signal transduction pathways and loss of PI3Kδ and BTK results in a profound B-cell defect. PI3Kδ and BTK also transmit signals from chemokine receptors (CXCR4/5) and adhesion molecules critical for malignant B-cell adhesion, migration, and retention in the tumor microenvironment. Disruption of PI3Kδ and BTK signaling has a synergistic effect on key biological activities necessary for malignant B-cell growth, survival, and migration.

Dual inhibition of PI3Kδ and BTK is also expected to induce a more pronounced expulsion of malignant B-cells from the protective tumor microenvironment. In a study done with idelalisib and ibrutinib, dual inhibition of PI3Kδ and BTK achieves greater inhibition of B-cell receptor- and chemokine receptor-stimulated adhesion compared with either agent alone. This occurs in a strongly synergistic manner, including at suboptimal drug concentrations. The PI3Kδ and BTK inhibitors target B-cell receptor signaling by different means; therefore, they may enhance each other's anticancer effect. Furthermore, the targeting of more than 1 key component of a pathway may overcome innate and overcome or prevent acquired (mono) therapy resistance.

BGB-10188 and zanubrutinib are highly selective and potent PI3Kδ and BTK inhibitors, respectively (Section 1.2.1). Improved antitumor activity was found with the combined treatment of BGB-10188 and zanubrutinib in mice subcutaneously xenografting TMD8 DLBL or JeKo-1 MCL tumor cells, and further improved antitumor activity was observed with a prolonged combination treatment (refer to BGB-10188 IB). Therefore, it is possibly optimal to explore the efficacy and safety of this combination.

1.3.2. Rationale for Combination of BGB-10188 and Tislelizumab in the Treatment of Advanced Solid Tumors

Inhibitors of PI3Kδ are being developed for the treatment of solid tumors because of the specific and critical functions of PI3Kδ in adaptive immune responses.

PI3Kδ is essential for the homeostasis and function of Foxp3+ Treg cells (Patton et al 2006). PI3Kδ-deficient mice develop colitis due to the reduced Treg cell functions (Patton et al 2006). Additionally, it was shown that PI3Kδ-inactivated Treg cells are impaired in mediating tumor immunosuppression. Loss of PI3Kδ activity, especially by specific deletion in Treg cells, can restrict the growth of transplanted tumors in mice (Ali et al 2014), providing a rationale for the evaluation of PI3Kδ inhibitors in solid tumors.

PD-1 is mainly expressed in activated T-cells, including CD8+ cytotoxic T-lymphocytes and CD4+ T-helper lymphocytes (McDermott and Atkins 2013). The PD-1 signaling cascade negatively regulates the T-cell receptor and attenuates T-cell proliferation and functional activities, leading to T-cell exhaustion. PD-1 expression is markedly up-regulated on tumor-infiltrating lymphocytes, while the expression of PD-L1 is significantly increased on tumor cells and tumor-associated immune cells in the presence of stimulating cytokines, such as interferon-gamma and interferon-alpha in the tumor microenvironment (Riley 2009), which is observed in

many types of human solid tumors. This body of evidence provides the basis for cancer immunotherapeutic intervention via the approach of antagonizing PD-1.

Significantly improved antitumor activity and prolonged survival were observed in the combination of BGB-10188 and mouse anti-PD-1 antibody in a CT26 colorectal tumor model (refer to BGB-10188 IB). The results of these nonclinical efficacy studies suggest that the PI3Kδ inhibitor BGB-10188 could significantly inhibit the growth of solid tumors in combination with PD-1 antibody.

1.3.2.1. Rationale for Combination of BGB-10188 and Tislelizumab in the Treatment of Platinum-Resistant Ovarian Cancer

Ovarian cancer (OC) is the eighth most common cancer in women worldwide. Globally, there were about 295,414 new cases and 184,799 deaths in 2018 (Bray et al 2018). Patients who developed disease progression < 6 months after the last dose of platinum are characterized as having platinum-resistant OC (PROC). The PROC population accumulates with lines of additional therapy, and almost all patients become resistant after 3 to 6 lines of prior chemotherapy.

For patients with PROC, standard cytotoxic chemotherapy with or without bevacizumab are generally recommended. The benefits of these agents are very limited, typically with an ORR of approximately 10%, a median PFS of 2.1 to 3.7 months, and median OS of 8.4 to 16.8 months. For the combination of chemotherapy with bevacizumab, the ORR improved to 27% for patients with PROC who received no more than 2 prior lines. However, the addition of bevacizumab resulted in an increased rate of Grade 2 or greater AEs, including hypertension (20% versus 7%) and proteinuria (2 versus 0%), as well as gastrointestinal perforation (2% versus 0%) (Stockler et al 2014). Thus, a more tolerable and effective alternative to the present therapy for patients with PROC is an urgent clinical need.

OC is a "cold tumor," characterized by low infiltration by $CD8^+$ T cells, activated $CD4^+$ T cells and increased infiltration by $PD\text{-}L1^+$ cells, known to promote peritoneal dissemination (Hamanishi et al 2015). The increased PD-L1 expression in post-chemotherapy ovarian tumor tissues indicates an opportunity of checkpoint inhibition in late-line setting of OC. However, single-agent pembrolizumab showed limited activity in heavily pretreated OC, with ORR as 5% in tumors with combined positive score<1 and 10.2% in tumors with combined positive score≥1 (Matulonis et al 2019). Up to date, anti-PD-1 monotherapy was only approved in limited patients with MSI-H or dMMR, or tumor mutational burden-high tumors (KEYTRUDA [pembrolizumab] [US Prescribing Information] 2023).

Studies have suggested that the frequencies of Treg cells in the epithelial OC samples are higher than those in the benign ovarian tumor samples (Zhu et al 2016). Large-scale meta-analysis suggested that increased Tregs was associated with poorer survival and correlated with more advanced stages of OC (Hao et al 2018). Those findings suggest that inhibition of Treg might bring clinical benefit in patients with OC. A recent study (NCT03860272) investigated the combination of balstilimab (anti-PD-1) and botensilimab (anti-CTLA-4) in PROC. With 24 patients enrolled, the results showed ORR as 33% and DOR not reached (median follow-up 6.9 months) (Bruno et al 2023). The promising antitumor activity indicates that Treg inhibition might has the potential to reverse immune cold environment and extend efficacy of checkpoint inhibition to immunotherapy insensitive tumors.

As of 05 April 2023, 4 patients with pretreated OC were enrolled in Part D of the current study. Two responders were reported. The preliminary efficacy of the study supported further evaluation of BGB-10188 combined with tislelizumab in the treatment of patients with PROC.

1.4. Dose Rationales

1.4.1. BGB-10188 in Monotherapy Escalation Phase (Part A)

Determination of the Starting Dose

The starting dose of BGB-10188 was determined based on animal toxicology results (detailed in Section 1.3.2). With a 10-fold safety margin, the maximum recommended starting dose (MRSD) in humans is calculated from rat MTD to be 145 mg once/day or 200 mg once/day (from dog MTD). By applying a more conservative approach using animal NOAEL, the MRSD was 48 mg once/day (from rat NOAEL) or 100 mg once/day (from dog NOAEL). Taken together, 60 mg once/day (being close to 48 mg once/day) is selected to be the starting dose in Part A monotherapy escalation phase. This dose level has more than 5 to 20 safety factors based on toxicity studies. The PK of BGB-10188 is being studied in the first-in-human study BGB-A317-3111-10188-101. The mean $t_{½}$ following a single dose was 7.3 hours in the 60 mg group and 11.2 hours in the 120 mg group. PK results showed that 2 peaks in the plasma concentration-time curve were observed in 7 of 9 patients after dosing (refer to Section 1.2.3). One ≥ Grade 3 treatment-related TEAE (upper respiratory tract infection) and 1 serious TEAE (acute myocardial infraction) were reported in 1 patient (7.1%) each as of the data cutoff date of 19 July 2021. No TEAEs leading to death were reported (refer to Section 1.2.4).

Prediction of Human Efficacious Dose Level for BGB-10188

The human PK parameters were predicted from animal PK results using classic allometric scaling methods; the efficacious plasma concentration levels of BGB-10188 were predicted from a panel of nonclinical pharmacodynamic or antitumor models. The simulated PK profiles at multiple dose levels suggested that at least 120 mg to 240 mg once daily of BGB-10188 were needed to achieve significant antitumor activity in the targeted population. Daily dose levels of 360 and 540 mg are also planned to evaluate safety and tolerability over a wide dose range.

1.4.2. BGB-10188 With Zanubrutinib in Combination Escalation Phase (Part B)

Approximately 3 dose levels of BGB-10188 will be selected based on data from the Part A monotherapy escalation phase and used in combination with zanubrutinib (160 mg twice daily) in the combination escalation phase of Part B. The dose levels of BGB-10188 may be adjusted per SMC's recommendation according to the safety, tolerability and PK data when combined with zanubrutinib. Both BGB-10188 and zanubrutinib are substrates of CYP3A and P-gp. Zanubrutinib is also a weak CYP3A inducer and may interact with BGB-10188 when given together. Therefore, while fixing the therapeutic dose level of zanubrutinib, the dose level of BGB-10188 will be further optimized and confirmed in the escalation cohorts, which will be used for the expansion phase.

1.4.3. BGB-10188 With Tislelizumab in Combination Escalation Phase (Part D)

When given with tislelizumab in the mouse model, the efficacious BGB-10188 concentration was about 3-fold lower than that using BGB-10188 alone. Simulated human PK profiles suggested that a daily dose level of 40 mg is sufficient to achieve predicted efficacious human exposure. Therefore, in Part D, which includes patients with solid tumor, 20 mg once/day of BGB-10188 was selected as the starting dose, ie, half of the predicted efficacious level of 40 mg once daily. The clinical exposure at the dose level of 120 mg, measured as AUC and C_{max} is 45.5- and 33.3-fold, respectively, lower than the nonclinical MTD exposure from the most sensitive species. Additional dose levels of 40, 80, 160, 320, and 540 mg in combination with tislelizumab (200 mg once every 3 weeks) will be evaluated to explore the optimal therapeutic dose of BGB-10188.

1.4.4. BGB-10188 With Tislelizumab in Combination Expansion Phase (Part E)

Two dose levels of BGB-10188 320 mg (orally daily) and 160 mg (orally daily) in combination with tislelizumab (200 mg intravenously once every 3 weeks) in patients with PROC have been selected for dose expansion. Dose selection of BGB-10188 in Part E was based on the totality of evidence available for clinical activity and safety from Part D, clinical PK/pharmacodynamics and supportive preclinical results. Refer to Section 1.5.3 and BGB-10188 IB for more detailed information. Both 160 and 320 mg were considered tolerable with preliminary efficacy, minimal PK overlapping, and fair target engagement. Alternate doses of BGB-10188 (eg, 80 mg orally once daily) or dose schedules may be added to Part E, depending on the benefit-risk of study drug and the various purposes of dose expansion, with the warrant and agreement from the Safety Monitoring Committee (SMC).

1.5. Benefit-Risk Assessment

1.5.1. Benefit-Risk Assessment for BGB-10188 Monotherapy in the Treatment of B-Cell Malignancies

In B-cell malignancies, PI3K pathway activity is significantly elevated and is driven by altered B-cell receptor signaling together with other co-stimulatory signals present in lymphoid tissues, such as chemokines and cytokines. PI3Kδ functions to integrate and transduce these signals from the microenvironment, thus promoting malignant B-cell proliferation, growth, survival, adhesion, and homing, making it an attractive drug target for B-cell malignancies. BGB-10188 has been shown to impede PI3Kδ activity and to inhibit lymphoma cancer cell growth and survival in nonclinical studies. BGB-10188 is a potent, selective, orally active PI3Kδ inhibitor.

In toxicity studies in rats and dogs, BGB-10188 related effects included hypersensitivity, hepatotoxicity, myeloid hyperplasia, lymphoid depletion, and cardiovascular event. It is possible that subjects participating in the current protocol could experience events similar to those that occurred in animals. These types of effects are readily monitored clinically and will be followed via frequent assessments of subject symptoms and laboratory parameters in the current study. Limited clinical safety data indicated that BGB-10188 appears to be well tolerated in patients with B-cell malignancies (Section 1.2.4).

As of 05 February 2024, 34 patients had received BGB-10188 monotherapy at doses of 60 mg/day (n = 5), 120 mg/day (n = 5), 240 mg/day (n = 8), 360 mg/day (n = 6), and 540 mg/day

(n = 10). Twenty-one patients were enrolled in Australia and 13 patients in China. Two DLT events have been observed: one patient in BGB-10188 360 mg monotherapy cohort had Grade 3 hepatic function abnormal lasting > 7 days, and another patient in BGB-10188 540 mg monotherapy cohort experienced Grade 3 hypertriglyceridemia. A total of 28 patients (82.4%) experienced adverse events assessed as related to BGB-10188. The most commonly (≥ 15%) occurring events by PT were Diarrhoea (9 patients, 26.5%) and Anaemia and Neutrophil count decreased (6 patients each, 17.6%). Nine patients (26.5%) were identified as having treatment-related adverse events ≥ Grade 3 in severity. No adverse events leading to treatment discontinuation or fatal adverse events were reported.

PI3Kδ inhibitors, such as idelalisib and copanlisib, have been approved for a variety of B-cell malignancies (idelalisib: relapsed CLL, copanlisib: relapsed FL) in the USA and Europe. Idelalisib has hepatotoxicity, diarrhea or colitis, pneumonitis, infection, and intestinal perforation as a black box warning. The most common adverse reactions (incidence ≥ 20%) in patients treated with idelalisib in the monotherapy trials are diarrhea, fatigue, nausea, cough, pyrexia, abdominal pain, pneumonia, and rash. The most common adverse reactions (≥ 20%) to copanlisib are hyperglycemia, diarrhea, decreased general strength and energy, hypertension, leukopenia, neutropenia, nausea, lower respiratory tract infection, and thrombocytopenia. The GLP toxicity studies demonstrated a bigger safety margin than idelalisib and copanlisib by comparing the exposure of NOAEL in GLP toxicity studies with the exposure of the approved or predicted efficacious dose in human. In summary, BGB-10188 is a novel PI3Kδ inhibitor with high selectivity and has a favorable safety profile in nonclinical studies over those approved PI3Kδ inhibitors, and no adverse drug reactions have been identified based on limited clinical safety data, which are promising and warrants the continuation of testing of the compound in human.

1.5.2. Benefit-Risk Assessment for the Combination of BGB-10188 and Zanubrutinib in the Treatment of B-Cell Malignancies

In vivo studies showed that BGB-10188 induced dose-dependent antitumor effects against Farage DLBCL xenografts engrafted either subcutaneously or systemically in mice. In addition, BGB-10188 in combination with a BTK inhibitor (zanubrutinib) showed therapeutic effects in TMD8 DLBCL and JEKO-1 MCL subcutaneous xenografts at doses of 10 to 30 mg/kg. No specific concerns were identified in the vital functions of the central nervous system (CNS) or respiratory system in safety pharmacology and toxicity studies in rats and dogs (refer to the BGB-10188 IB). The GLP toxicity studies demonstrated a bigger safety margin than idelalisib and copanlisib by comparing the exposure of NOAEL in GLP toxicity studies with the exposure of the approved or predicted efficacious dose in human.

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 antitumor activity in advanced B-cell malignancies, including CLL, MCL, WM, hairy cell leukemia, DLBCL, FL, and MZL. Approximately 2772 patients have been enrolled worldwide in completed and ongoing clinical trials evaluating zanubrutinib and have received ≥ 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 R/R mature B-cell malignancies.

As of data cutoff date of 05 February 2024, safety data are available from 4 patients exposed to BGB-10188 240 mg once per day in combination with zanubrutinib 160 mg twice per day. Two DLTs occurred in the extended DLT window (ie, between Day 29 and Day 56) due to ALT and AST increased and persisted for more than 7 days in 2 patients.

After BGB-10188 interruption, 1 patient (Patient ID [redacted] recovered gradually and has restarted BGB-10188 on a reduced dose of 120 mg once per day with zanubrutinib 160 mg twice per day. After BGB-10188 interruption, Patient ID [redacted] received steroid treatment and raised ALT/AST recovered gradually, and patient has been reintroduced to BGB-10188 on a reduced dose of 120 mg once per day with zanubrutinib 160 mg twice per day. One patient (25%) experienced a treatment-emergent SAE (Grade 4 Acute myeloid leukaemia, assessed by the investigator as not related to study drugs). No TEAE leading to death was reported.

Based on the experience with patients exposed to BGB-10188 240 mg once per day in combination with zanubrutinib 160 mg twice per day in Part B, and for reasons of development strategy, the Sponsor has suspended further exploration of this Part.

1.5.3. Benefit-Risk Assessment for the Combination of BGB-10188 and Tislelizumab in the Treatment of Advanced Solid Tumors

The results of nonclinical efficacy studies suggest that BGB-10188 could significantly inhibit the growth of solid tumors in combination with the PD-1 antibody. In the CT26WT mouse colon cancer syngeneic model, BGB-10188 combined with anti-mouse PD-1 antibody muCh15mt significantly increased the TGI and TF% compared with a single agent alone at doses of 10 to 30 mg/kg (TGI increased to 72% to 88% versus 21% to 56% in single agent groups; TF% increased to 54% to 71% versus 0 to 37% in single agent groups) (BGB-10188 IB). The GLP toxicity studies demonstrated a bigger safety margin than idelalisib and copanlisib by comparing the exposure of NOAEL in GLP toxicity studies with the exposure of the approved or predicted efficacious dose in human. In summary, BGB-10188 is a novel PI3Kδ inhibitor with best selectivity and improved safety profile shown in nonclinical studies, which is promising and warrants the testing of the compound in humans.

Tislelizumab is being developed for the treatment of human malignancies in multiple organs and tissues as monotherapy or in combination with other therapies. The overall safety experience with tislelizumab is based on experience in 2377 patients as a monotherapy and 2019 in combination with chemotherapy as of the data cutoff date of 27 October 2023. The safety profile of tislelizumab given in combination with other anticancer medications is generally consistent with the safety profile of similar drug-class combinations using other agents.

As of 05 February 2024, 43 patients have received BGB-10188 at doses of 20 mg/day (n = 5), 40 mg/day (n = 5), 80 mg/day (n = 6), 160 mg/day (n = 11), 320 mg/day (n = 10), and 540 mg/day (n = 7) in combination with tislelizumab 200 mg once every 3 weeks. One patient in this arm of the study received BGB-10188 but discontinued before receiving tislelizumab. Two patients experienced DLT events (Grade 3 Rash in 1 patient receiving BGB-10188 540 mg in combination with tislelizumab; Grade 3 Aspartate aminotransferase increased in 1 patient receiving BGB-10188 at a dose of 320 mg) that are assumed by the investigator to be related to BGB-10188. A third patient receiving BGB-10188 160 mg in combination with tislelizumab 200 mg (Patient ID [redacted] died due to Pneumonia and Haemorrhage intracranial, which

were both related to BGB-10188. For more details about this DLT event, please refer to Section 5.2.3.8 of the BGB-10188 Investigator's Brochure.

Overall, the dataset is currently small, and data are continuing to emerge in this ongoing study. However, to date, no significant actions related to safety were taken by the sponsor for the BGB-10188 study.

Given the high unmet medical needs and limited efficacy of current standard of care in PROC and given the promising data in nonclinical studies and emerging efficacy/tolerable safety in clinical studies (Section 1.3.2), the benefit-risk assessment of the combination of BGB-10188 with tislelizumab in PROC is considered favorable. Part E will be conducted in order to further define the recommended Phase 2 dose and assess the potential benefit and safety of tislelizumab combined with BGB-10188 for patients with PROC. To ensure the safety of enrolled patients, ongoing safety monitoring would be conducted. Additionally lower doses of BGB-10188 (eg, 80 mg) may be considered based on emerging clinical evidence (Section 1.4.4).

1.6. Study Conduct

This study will be conducted in compliance with the protocol approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and in accordance with Good Clinical Practice (GCP) standards.

2. STUDY OBJECTIVES

2.1. Study Objectives

Part A: BGB-10188 Monotherapy Dose Escalation in Patients With Relapsed/Refractory (R/R) Mature B-Cell Malignancies

Primary:

- To determine the maximum tolerated dose and the recommended dose for expansion (RDFE) of BGB-10188 as monotherapy
- To assess the safety and tolerability of BGB-10188 as monotherapy

Secondary:

- To evaluate the preliminary antitumor activity of BGB-10188 monotherapy as measured by investigator-assessed overall response rate
- To characterize the pharmacokinetic profiles of BGB-10188 as monotherapy

Exploratory:

- To explore relationships between BGB-10188 concentrations and corrected QTcF intervals
- To characterize the pharmacodynamic profiles of BGB-10188 after a single dose and at steady state
- To explore the relationships between biomarkers and mechanisms of resistance and preliminary antitumor activity of BGB-10188 monotherapy

Part B: BGB-10188 + Zanubrutinib Dose Escalation in Patients With R/R Follicular Lymphoma, R/R Mantle Cell Lymphoma, or R/R Diffuse Large B-Cell Lymphoma

Primary:

- To determine the maximum tolerated dose and the RDFE of BGB-10188 in combination with zanubrutinib
- To assess the safety and tolerability of BGB-10188 in combination with zanubrutinib

Secondary:

- To evaluate the preliminary antitumor activity of BGB-10188 in combination with zanubrutinib as measured by investigator-assessed overall response rate, duration of response (DOR), and time to response
- To characterize the pharmacokinetic profiles of BGB-10188 in combination with zanubrutinib

Exploratory:

- To characterize the pharmacokinetic profile of zanubrutinib when given in combination with BGB-10188
- To characterize the pharmacodynamic profiles of BGB-10188 in combination with zanubrutinib
- To explore the relationships between biomarkers and mechanisms of resistance and preliminary antitumor activity of BGB-10188 in combination with zanubrutinib

Part C: BGB-10188 + Zanubrutinib Dose Expansion in Patients With R/R Follicular Lymphoma, R/R Mantle Cell Lymphoma, or R/R Diffuse Large B-Cell Lymphoma

Primary:

- To evaluate the preliminary antitumor activity of BGB-10188 in combination with zanubrutinib as measured by investigator-assessed overall response rate

Secondary:

- To evaluate the preliminary antitumor activity of BGB-10188 in combination with zanubrutinib as measured by investigator-assessed duration of response, time to response, and progression-free survival
- To assess the safety and tolerability of BGB-10188 in combination with zanubrutinib
- To characterize the pharmacokinetic profiles of BGB-10188 in combination with zanubrutinib

Exploratory:

- To evaluate the preliminary antitumor activity of BGB-10188 in combination with zanubrutinib as measured by overall survival
- To explore the relationships between biomarkers and mechanisms of resistance and preliminary antitumor activity of BGB-10188 in combination with zanubrutinib at the RDFE
- To characterize the pharmacokinetic profile of zanubrutinib when given in combination with BGB-10188
- To characterize the pharmacodynamic profiles of BGB-10188 in combination with zanubrutinib at the RDFE

Part D: BGB-10188 + Tislelizumab Dose Escalation in Patients With Advanced Solid Tumors

Primary:

- To determine the maximum tolerated dose and the RDFE of BGB-10188 in combination with tislelizumab
- To assess the safety and tolerability of BGB-10188 in combination with tislelizumab

Secondary:

- To evaluate the preliminary antitumor activity of BGB-10188 in combination with tislelizumab as measured by investigator-assessed overall response rate, duration of response, disease control rate, and time to response
- To characterize the pharmacokinetic profiles of BGB-10188 in combination with tislelizumab

Exploratory:

- To assess host immunogenicity to tislelizumab in combination with BGB-10188
- To assess the pharmacokinetics of tislelizumab in combination with BGB-10188
- To characterize the pharmacodynamic profiles of BGB-10188 in combination with tislelizumab
- To explore the relationships between biomarkers and mechanisms of resistance and preliminary anticancer activity of BGB-10188 in combination with tislelizumab

Part E: BGB-10188 + Tislelizumab Dose Expansion in Patients With Platinum-Resistant Ovarian Cancer (PROC)

Primary:

- To evaluate the preliminary antitumor activity of BGB-10188 in combination with tislelizumab in PROC as measured by the investigator-assessed overall response rate.
- To assess the safety and tolerability of BGB-10188 in combination with tislelizumab

Secondary:

- To evaluate the preliminary antitumor activity of BGB-10188 in combination with tislelizumab as measured by investigator-assessed duration of response, progression-free survival, disease control rate, clinical benefit rate, and time to response
- To evaluate the preliminary antitumor activity of BGB-10188 in combination with tislelizumab as measured by locally assessed carcinoma antigen-125 (CA-125) response rate per Gynecological Cancer Intergroup for CA-125 changes
- To characterize the pharmacokinetic profiles of BGB-10188 in combination with

tislelizumab

Exploratory:

- To assess host immunogenicity to tislelizumab in combination with BGB-10188
- To characterize the pharmacodynamic profiles of BGB-10188 in combination with tislelizumab at the recommended doses for expansion
- To explore the relationships between biomarkers and mechanisms of resistance and preliminary anticancer activity of BGB-10188 in combination with tislelizumab at the RDFE

3. STUDY DESIGN

3.1. Summary of Study Design

This is an open-label, multicenter, dose escalation and dose expansion study to evaluate the safety and tolerability, determine the MTD and RDFE, and evaluate the preliminary antitumor activity of the following:

- BGB-10188 monotherapy in patients with R/R CLL/SLL, R/R MZL, R/R FL, R/R MCL, or R/R DLBCL
- BGB-10188 in combination with zanubrutinib in patients with R/R FL, R/R MCL, or R/R DLBCL
- BGB-10188 in combination with tislelizumab in patients with advanced solid tumors.

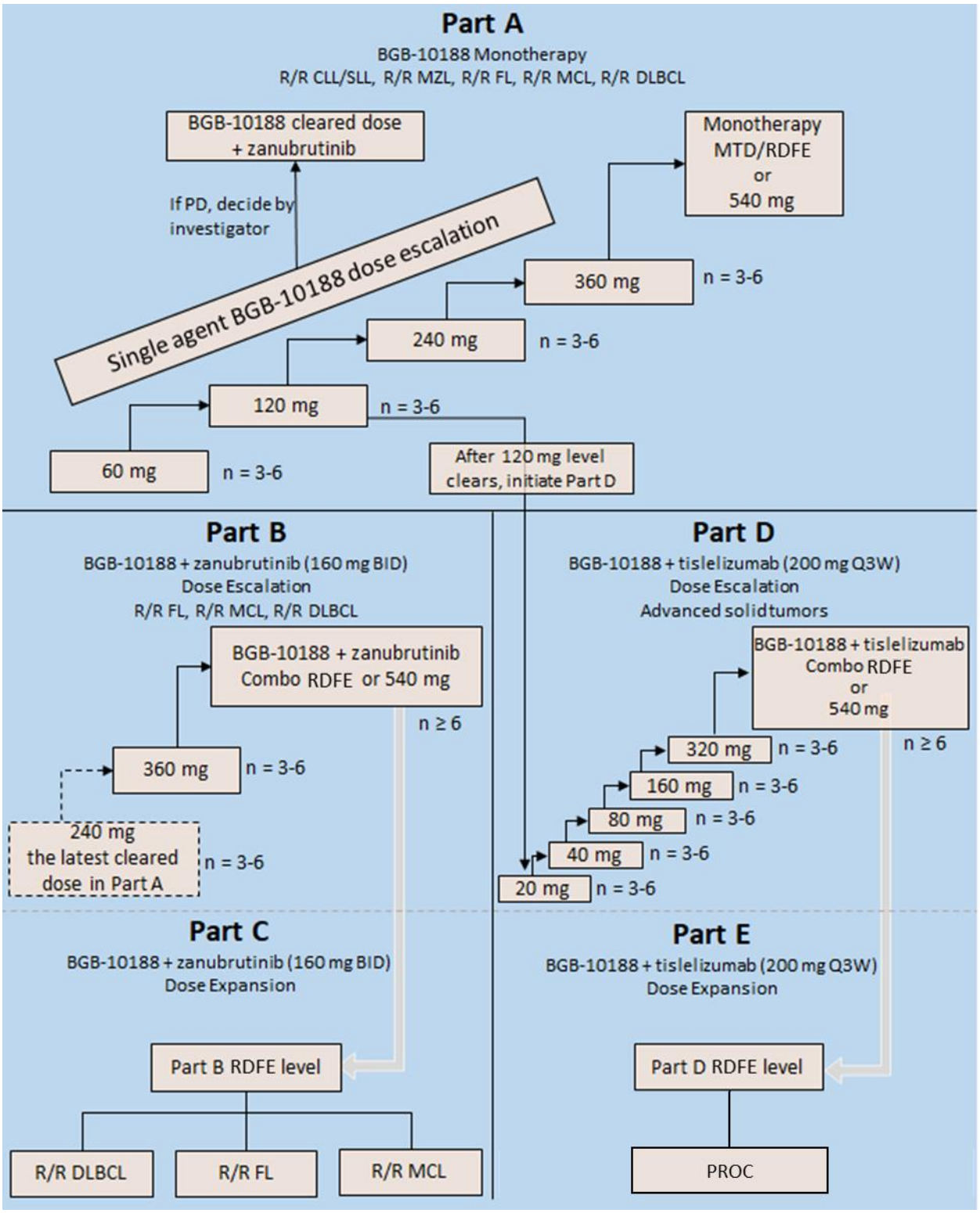
The study will be conducted in 4 parts, which are as follows:

- Part A, a dose escalation phase to determine the MTD/RDFE of BGB-10188 monotherapy in patients with R/R mature B-cell malignancies
- Part B, planned as a dose escalation phase to determine the MTD/RDFE of BGB-10188 in combination with zanubrutinib in patients with R/R FL, R/R MCL, and R/R DLBCL.
- Part C, a dose expansion phase for evaluation of BGB-10188 in combination with zanubrutinib at the RDFE in patients with R/R FL, R/R MCL, and R/R DLBCL
- Part D, a dose escalation phase to determine the MTD/RDFE of BGB-10188 in combination with tislelizumab in patients with advanced solid tumors
- Part E, a dose expansion phase for evaluation of BGB-10188 in combination with tislelizumab at the RDFEs for patients with PROC

Part C, a dose expansion phase for evaluation of BGB-10188 in combination with zanubrutinib at the RDFE in patients with R/R FL, R/R MCL, and R/R DLBCL, was originally planned but was cancelled by the sponsor and will not be initiated.

The study design schematic is presented in Figure 1. More details about Part E, please see Figure 2. A total of approximately 84 patients (excluding patients for China verification parts) are expected to be enrolled in Parts A, B, and D, the dose escalation portions of the study. The sample size for China verification parts will be based on the escalation status in Part A and Part D. For Part E, approximately 30 to 50 patients with PROC are expected to be enrolled.

Figure 1: Study Schema



Abbreviations: CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MTD, maximum tolerated dose; MZL, marginal zone lymphoma; PD, progressive disease; PROC, platinum-resistant ovarian cancer; RDFE, recommended dose for expansion; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.

Part C, a dose expansion phase for evaluation of BGB-10188 in combination with zanubrutinib at the RDFE in patients with R/R FL, R/R MCL, and R/R DLBCL, was originally planned but was cancelled by the sponsor and will not be intiated.

For all study procedures, see Section 7 and Appendix 1 through Appendix 4.

Part A is designed to determine the MTD and the RDFE of BGB-10188 as monotherapy in patients with R/R CLL/SLL, R/R MZL, R/R FL, R/R MCL, and R/R DLBCL. Approximately 5 dose levels of BGB-10188 monotherapy will be tested: 60 mg once daily, 120 mg once daily, 240 mg once daily, 360 mg once daily, and 540 mg once daily. Additional dose levels can be added if deemed appropriate. Part B will be initiated at the latest cleared dose of monotherapy to escalated doses to determine the MTD/RDFE of BGB-10188 in combination with zanubrutinib 160 mg twice daily in R/R FL, R/R MCL, and R/R DLBCL. After a dose level of BGB-10188 is proven to be safe in Part A, the same dose level of BGB-10188 in combination with zanubrutinib could be opened. The dose levels of BGB-10188 may be adjusted per SMC's recommendation according to the safety, tolerability, and PK data when combined with zanubrutinib. Additional dose levels could be added by the SMC based on safety, tolerability, and PK data. When the dose of 120 mg once daily in Part A has been demonstrated safe, Part D, BGB-10188 dose escalation in combination with tislelizumab 200 mg once every 3 weeks in patients with advanced solid tumors, will be triggered. In Part D, approximately 6 dose levels of BGB-10188 will be tested: 20 mg once daily, 40 mg once daily, 80 mg once daily, 160 mg once daily, 320 mg once daily, and 540 mg once daily. The dose levels and schedules of BGB-10188 may be adjusted according to the safety and exposure results in Part A, and additional dose levels could be further explored.

Dose expansion of BGB-10188 in combination with tislelizumab (Part E) will be explored after the RDFE of BGB-10188 in combination with tislelizumab (Part D) has been determined. In Part E, patients with PROC that have progressed on/after prior anticancer treatment and checkpoint inhibitor naïve will be randomized at a 2:1 ratio in an open-label setting to either BGB-10188 160 mg once daily (approximately 20 patients, final patients number may change) or 320 mg once daily (approximately 10 patients, final patients number may change) in combination with tislelizumab (200 mg once every 3 weeks).

Part C, a dose expansion phase for evaluation of BGB-10188 in combination with zanubrutinib at the RDFE in patients with R/R FL, R/R MCL, and R/R DLBCL, was originally planned but was cancelled by the sponsor and will not be initiated.

In Parts A and B, a cycle is defined as 28 days in length. In Part D, a cycle is defined as 21 days in length except for Cycle 1, which is 28 days in length, due to the DLT assessment period. In Part E, a cycle is defined as 21 days in length.

BGB-10188 will be administered orally, once daily until unequivocal progression, unacceptable toxicity, death, withdrawal of consent, lost to follow-up, end of study, investigator's decision, or the study is terminated by sponsor, whichever comes first. Patients with disease progression in Part A can receive the cleared dose of BGB-10188 in combination with zanubrutinib at the investigator's discretion based on the local guidance and zanubrutinib prescribing information that the patients can benefit from treatment in combination with zanubrutinib (see Section 7.6.1).

Zanubrutinib 160 mg will be administered twice daily until disease progression, unacceptable toxicity, death, withdrawal of consent, lost to follow-up, end of study, investigator's decision, or the study is terminated by sponsor, whichever comes first.

Tislelizumab 200 mg will be administered intravenously on C1D8 and Day 1 of each subsequent cycle in Part D and on Day 1 of each cycle in Part E until disease progression, unacceptable toxicity, death, withdrawal of consent, lost to follow-up, end of study, investigator's decision, or the study is terminated by sponsor whichever comes first. The decision to continue tislelizumab beyond the initial investigator-assessed progression must be agreed upon with the medical monitor and documented in the study records.

A Bayesian model-based dose escalation approach will be used for dose escalation and MTD determination of BGB-10188 monotherapy. Modified 3 + 3 design and dose escalation criteria will be used for combination therapy with zanubrutinib 160 mg twice daily. A Bayesian model-based dose escalation approach will be used for dose escalation and MTD determination of the combination therapy with tislelizumab.

Dose Verification in Chinese Patients (Part A and Part D)

Before enrollment of patients in China for Part B and Part E, the safety and tolerability of BGB-10188 as monotherapy (Part A) and in combination with tislelizumab (200 mg once every 3 weeks) (Part D) will be assessed in Chinese patients in accordance with detailed verification rules described in Section 3.2.2. The RDFE for Chinese patients will be determined according to the SMC recommendation based on the totality of the safety data and preliminary efficacy data of BGB-10188 as monotherapy and when combined with tislelizumab 200 mg.

Dose-Limiting Toxicity

In Parts A, B, and D, patients will be evaluated for DLTs during Cycle 1. Patients will continue to be evaluated for late-onset DLTs events up to 8 weeks due to late-onset toxicities that have been associated with first-generation PI3Kδ inhibitors. A DLT is a toxicity or AE defined as meeting at least one of the following criteria listed in Section 3.2.4 and is not due to alternative causes (such as underlying illness, concurrent illness, or concomitant medication). The SMC will review the accumulated safety data and model results after the last patient (decided by the sponsor/SMC) or ≥ 3 DLT-evaluable patients of the current cohort, whichever occurs earlier, have completed the 28-day observation period and make a recommendation on whether or not to proceed to the next dose level for the next cohort. Sponsor will make the final decision based on the recommendation of the SMC. The RDFE may not be the MTD since targeted therapies can achieve the desired antitumor effect at doses lower than the MTD.

If a patient does not receive treatment with ≥ 75% of the expected dose for reasons other than treatment-related toxicity within the DLT observation period, then an additional patient will be enrolled. However, all patients that receive ≥ 1 dose of study drug will be included in the overall analysis of safety and tolerability.

Study Assessments

Assessments of disease status during the study will include symptom-directed physical examination; disease-related constitutional symptoms (as necessary); complete blood count (CBC); bone marrow examination (as necessary); gastrointestinal examination (as necessary); and imaging scans.

For patients with CLL, disease response will be determined in accordance with the 2018 iwCLL guidelines (Hallek et al 2018) with modification for treatment-related lymphocytosis (Cheson et al 2012). For patients with NHL (including SLL, MCL, MZL, DLBCL, and FL), disease response will be determined in accordance with the Lugano Classification for NHL (Cheson et al 2014). Patients in Parts A and B with NHL (ie, SLL, MZL, MCL, FL, or DLBCL) will undergo positron emission tomography (PET)/computed tomography (CT) imaging at baseline; a separate CT scan of diagnostic quality should be performed in addition to the PET/CT imaging if the PET/CT imaging is not of diagnostic quality. If PET-avid disease is detected, then subsequent tumor assessments should be conducted with PET/CT-based imaging. Patients in Parts A and B with NHL without PET-avid disease, as well as patients with CLL, should undergo tumor assessments with CT-based imaging. For patients with B-cell malignancies, (Parts A and B), tumor imaging will be performed every 8 weeks for the first 24 weeks, every 12 weeks for the next 24 weeks, and then every 16 weeks thereafter. For patients with advanced solid tumors (Parts D and E), tumor imaging will be performed at Week 10 (Part D) or Week 9 (Part E) and approximately every 9 weeks (± 7 days) thereafter, based on Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1; Eisenhauer et al 2009; Appendix 17). Assessments will be performed until disease progression, use of alternative anticancer therapy, withdrawal of consent, death, lost to follow-up, or end of study, whichever occurs first. Patients with disease progression in Part A can receive the cleared dose of BGB-10188 in combination with zanubrutinib at the investigator's discretion based on the local guidance and zanubrutinib prescribing information that the patients can benefit from treatment in combination with zanubrutinib. This should be discussed and approved by the sponsor.

Blood samples for BGB-10188 PK and pharmacodynamics analyses will be collected after single and repeated doses at specified timepoints in Part A through Part E. In Part A only, all patients will receive a single dose of BGB-10188 followed by a washout period of 7 days.

Patients will be evaluated for AEs (all grades, according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 [NCI-CTCAE v5.0]) and SAEs. Patients who, at time of progression, have an ongoing AE that leads to treatment discontinuation, will be followed until the event resolves, the investigator assesses the event as stable, the patient is lost to follow-up, or the patient starts a different anticancer therapy.

3.2. Details of Dose Escalation

After completing all screening activities, eligible patients will be enrolled.

3.2.1. Starting Dose and Dose Escalation Approach

In Part A, dose escalation will occur for 5 proposed, sequentially increasing dose levels of BGB-10188 monotherapy. Each dose level of BGB-10188 that is evaluated may be referred to as a cohort or dose level. Dose escalation will begin with BGB-10188 at 60 mg once daily. The dose escalation phase will cease once the MTD or RDFE for BGB-10188 monotherapy has been determined. Dose verification in Chinese patients will be performed, starting with the dose that has been identified as safe or as the RDFE in Part A. The specific dose-verification rules are described in Section 3.2.2.

In Part B, the initial dose of BGB-10188 for the combination therapy evaluation will be the latest cleared dose of BGB-10188 monotherapy. In Part D, dose escalation of 6 proposed dose levels

of BGB-10188 with tislelizumab may begin with 20 mg BGB-10188 after the dose level of 120 mg in Part A has been determined to be safe, ie, this dose level as a monotherapy has met the criteria for dose escalation as described below (Section 3.2.2). The dose escalation phases (Part B and Part D) will cease once the RDFE for BGB-10188 in combination with zanubrutinib or tislelizumab has been determined for the respective parts. Any remaining patients will continue with their originally assigned dosing regimen until they meet a discontinuation criterion. Intrapatient dose escalation may be considered in Part A, Part B, or Part D either when the next higher dose has been deemed to be safe (eg, the SMC has voted to escalate to 2 doses higher of the initially assigned dose of such patients), or when the MTD has been identified. This must be discussed with and approved by the sponsor. Dose verification in Chinese patients will be performed and will start with the dose regimens that have been identified as safe or as the RDFE in Part D. The specific dose-verification rules are described in Section 3.2.2.

3.2.2. Rules for Dose Escalation and Dose Verification

Part A Monotherapy and Part D Combination Therapy With Tislelizumab

A Bayesian model-based dose escalation approach will be used to assist dose escalation and MTD determination for BGB-10188 monotherapy in Part A and for combination therapy with tislelizumab in Part D. Two statistical models will be used: A Bayesian logistic regression model (BLRM, Neuenschwander et al 2008) will be used to model the dose relationship with the early-onset DLT events that occur within the 28-day observation period; additionally, considering the late onset of specific DLT events from 28 days to 8 weeks and to provide additional protection against overdosing, a Bayesian proportional hazard (BPH) model similar to Tighiouart et al (2014) will be used to account for the overall toxicity level until 8 weeks. The BPH models will incorporate time-to-event data and do not require that all patients in the current cohort complete the entire observation period before a new cohort can be recruited. More details about model-based dose escalation approaches are provided in Section 9.

A cohort in the dose escalation step is defined as a set of approximately 3 patients sequentially enrolled and treated at the dose level recommended for the cohort. One or more cohorts of patients can be recruited for each dose level evaluated.

Before each dose recommendation for a new cohort, the statistical models will be run based on all the event data and observation period (for the BPH model) collected for the current and the previous dose levels. Dose escalation/de-escalation recommendation will be based on the estimated distribution of DLT probabilities for each candidate dose level. The dose with maximum probability within the targeted range of early-onset DLT rate while controlling the overdosing probabilities taking into account both early- and late-onset DLT events will be recommended.

At the end of the dose escalation step, the MTD recommended is the dose level with the highest probability that its DLT rate falls into the target toxicity interval (16% to 33%) while the probabilities that it falls into the overdosing interval (≥ 33%) are controlled. Further details are provided in Section 9.1. Skipping an untested dose level is generally not allowed in the escalation process. The dose recommendation by the models is non-binding. The SMC, which includes investigators, the medical monitor, and study team members from Pharmacovigilance/ Drug Safety, Clinical Pharmacology, and Biostatistics with other members as appropriate, will review the accumulated safety data and model result after the last patient (decided by

sponsor/SMC) or ≥ 3 patients of the current cohort, whichever occurs earlier, have completed the 28-day observation period and make the recommendation on the dose level for the next cohort based on the totality of data as described in the study assessment section. Sponsor will make the final decision based on the recommendation of the SMC (refer to the SMC charter for more details).

Part B Combination Therapy With Zanubrutinib

For the BGB-10188 dose escalation in combination with zanubrutinib in Part B, dose escalation will occur in accordance with the following modified 3 + 3 dose escalation rules.

A minimum of 3 patients will be initially enrolled per dose level.

- If none of the first 3 evaluable patients enrolled in a given dose level experience a DLT, dose escalation may proceed.
- If 1 of the first 3 evaluable patients enrolled in a given dose level experiences a DLT, additional patients (for a minimum of 6 evaluable patients) will be enrolled in that cohort.
    - If less than one-third of evaluable patients in a given dose level experiences a DLT (eg, DLTs in fewer than 2 of 6 patients), escalation will proceed to the next higher dose level.
    - If a DLT is observed in ≥ one-third or more of patients (eg, 2 or more in 6 patients or less), the MTD will have been exceeded and dose escalation will be stopped.
- Additional patients (for a minimum of 6 evaluable patients) will be assessed for DLTs at the preceding dose level (if a minimum of 6 evaluable patients had not already been assessed at that dose level).
    - If the MTD is exceeded at a given dose level, the next highest dose level at which less than one-third of evaluable patients in a given cohort experiences a DLT (eg, DLTs in fewer than 2 of 6 patients) will be declared the MTD.
    - If less than one-third of evaluable patients (eg, DLTs in fewer than 2 of 6 patients) at the highest dose level experience a DLT, this dose level will be declared the maximum administered dose.

All available safety data, including AEs, laboratory assessments, and PK analyses (as available), will be reviewed by the SMC. On the basis of a review of safety data and available preliminary PK data, dose escalation may be halted or modified as deemed appropriate.

Based on the safety data of the patients exposed to BGB-10188 240 mg once per day in combination with zanubrutinib 160 mg twice per day in Part B, the SMC recommended that recruitment in Part B combination therapy be placed on hold. The Sponsor decided to suspend development of this Part.

Dose Verification in Chinese Patients (Part A and Part D)

Based on the safety results of Part A and Part D conducted in Australia, the safety and PK characteristics of the BGB-10188 dose levels that are identified as safe as monotherapy and when combined with tislelizumab 200 mg once every 3 weeks will be assessed in Chinese

patients with B-cell malignancies and advanced malignant solid tumors. Other doses may be further explored based on the safety results and necessity.

A dose verification study in China will occur in Part A and Part D. DLT will be assessed among evaluable patients within Cycle 1 and within a prolonged window for some events. The SMC will review the accumulated data after the last patient (decided by the sponsor/SMC) or ≥ 3 patients of the current cohort, whichever occurs earlier, have completed the 28-day observation period. The SMC will make a recommendation on whether or not to proceed to the next dose level for the next cohort. Approximately 3 to 6 patients will be enrolled in each cohort to assess DLT in Chinese patients with BGB-10188 monotherapy; these patients will be started at the dose that most recently identified by the SMC as safe in Part A in Australia and with BGB-10188 starting at the dose most recently identified by the SMC as safe when combined with tislelizumab 200 mg once every 3 weeks in Part D in Australia. The SMC will recommend the next dose for subsequent patients. The general dose recommendation rules will follow the modified 3 + 3 design as in Part B.

By the time of initiating the China sites, if the RDFE has been identified in Australia sites for Part A and Part D, the China sites will enroll 3 to 6 patients with a starting dose at the RDFE level to confirm the safety, tolerability, PK, and pharmacodynamic profile in Chinese patients. The general dose-confirmation rules are as follows:

- If no DLT is observed during the DLT assessment window in the first 3 patients in this cohort (0/3), the current dose may be confirmed as the MTD.
- If 1 DLT is observed in the first 3 patients in this cohort (1/3), 3 additional patients will be enrolled for a total of 6 patients. If no additional patients experience DLT(s) (1/6), the current dose will be confirmed as the MTD.
- If > 1 DLT is observed in the first 3 to 6 patients during the DLT assessment window, the MTD is considered exceeded, and the dose will be de-escalated to the preceding lower level and tested repeatedly following the abovementioned dose-confirmation rules.

If needed, a decision to proceed to other dose levels could be made by the SMC along with the sponsors and investigators.

3.2.3. Assessment of Dose-Limiting Toxicity

For initial dose-finding recommendations, AEs will be assessed per the DLT criteria below (Section 3.2.4) during the 28-day DLT assessment window, which starts with the first day of study drug administration on C1D1.

Patients will be considered evaluable for DLTs if they: 1) received ≥ 75% of each scheduled study drug administration during the DLT assessment window, and/or 2) experienced a DLT.

Patients will be considered not evaluable for DLTs, if they: 1) were withdrawn from the study before completion of the DLT assessment window and did not experience a DLT, and 2) did not receive ≥ 75% of each scheduled study drug administration during the DLT assessment window and did not experience a DLT. Patients who are not DLT-evaluable must be replaced.

Clinically important or persistent AEs that are not part of the DLT criteria (Section 3.2.4) may also be considered a DLT following review by the SMC. For Part A, AEs that occur in the PK

washout period (from C1D-7 to C1D-1) will be reviewed by the SMC to decide whether the AEs may be considered DLTs. Additionally, any clinically significant AEs that occur after the DLT assessment window (eg, late imAE) for a given dose level, may be considered regarding subsequent dose escalation decisions. In such cases where patients have been safely dosed at the next dose level, additional dose escalation criteria (eg, increased minimum number of patients or expanded DLT assessment window) for subsequent dose levels will be considered by the SMC.

Any patient who experiences a DLT may be withdrawn from treatment.

3.2.4. Dose-Limiting Toxicity Definition

All toxicities or AEs will be graded according to the NCI-CTCAE v5.0.

DLT is defined as an AE that meets one of the following criteria:

- Event occurs **within 4 weeks (28 days)** after start of study drug administration on C1D1, is related to the investigational agent, and is not due to alternative causes (eg, underlying disease, concurrent disease, or concomitant treatment):
  a. Hematologic toxicity:
     - Grade 4 neutropenia lasting > 7 days
     - ≥ Grade 3 febrile neutropenia
     - ≥ Grade 3 thrombocytopenia with Grade ≥ 2 bleeding
     - Grade 4 thrombocytopenia lasting > 7 days
  b. Nonhematologic toxicity
     - ≥ Grade 3 event persistent for more than 7 days
     - Any Grade of intracranial hemorrhage
  c. Any toxicity that does not meet the abovementioned DLT criteria but which leads to discontinuation or dosing interruption of > 7 days of BGB-10188 or zanubrutinib prior to Day 28 is considered a DLT.
- Event occurs within a prolonged window up to 8 weeks (56 days) after starting BGB-10188 administration, is related to the investigational agent, and is not due to alternative causes (eg, underlying disease, concurrent disease, or concomitant treatment):
  - ≥ Grade 3 events of skin reaction, pneumonitis, colitis, diarrhea
  - Any Grade of ALT/AST increase lasting > 7 days

Note: For Part D only, the following AEs will not be considered DLTs:

- Grade 3 endocrinopathy that is adequately controlled by hormonal replacement
- Grade 3 tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumors)
- Grade 3 infusion-related AE that is transient (resolved within 6 hours of onset)

3.2.5. Recommended Dose For Expansion Determination

The RDFE may not be higher than the MTD (or maximum administered dose if the MTD is not reached) but may be lower. The SMC will review all available applicable data and make a recommendation as to the RDFE, with the choice ultimately made by the sponsor. The RDFE for Part A (BGB-10188 monotherapy), Part B (BGB-10188 + zanubrutinib), and Part D (BGB-10188 + tislelizumab) will be determined from safety, tolerability, PK, and any other relevant and available data that is obtained from the dose escalation phase. Once the RDFE is determined, that dose will then be evaluated in the dose expansion phases.

3.3. Details of Dose Expansion

The dose expansion phase, Part E (BGB-10188 + tislelizumab), will begin once the RDFE has been determined from Part D. Patients will be enrolled in each cohort in parallel. Each cohort will be evaluated independently for study endpoints and may be closed due to lack of preliminary anticancer activity or other reasons. In Part E, dose expansion will include patients with PROC in 2 arms, where 2 dose levels of BGB-10188 will be explored. Part C, a dose expansion phase for evaluation of BGB-10188 in combination with zanubrutinib at the RDFE in patients with R/R FL, R/R MCL, and R/R DLBCL, was originally planned but was cancelled by the sponsor and will not be initiated.

3.3.1. Study Design of Part E

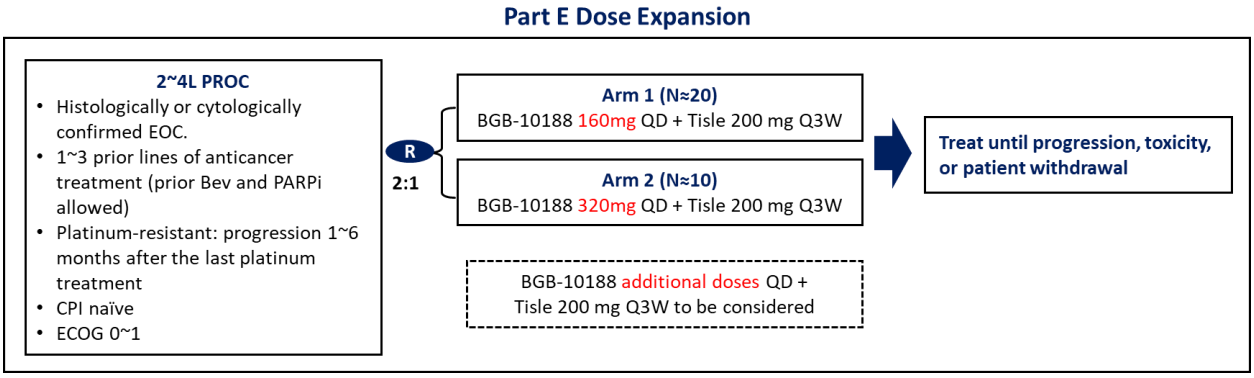
Part E is an open-label, randomized, multicenter, dose expansion phase to evaluate the safety and preliminary efficacy of BGB-10188 combined with tislelizumab in patients with PROC. Approximately 30 to 50 patients with PROC that have progressed on/after prior anticancer treatment, and CPI-naïve will be randomized at a 2:1 ratio to receive either BGB-10188 (160 mg once daily) plus tislelizumab (200 mg once every 3 weeks) or BGB-10188 (320 mg once daily) plus tislelizumab (200 mg once every 3 weeks) until disease progression, intolerance, or patient withdrawal for other reasons.

- Arm 1: BGB-10188 160 mg orally once daily + tislelizumab 200 mg intravenously once every 3 weeks
- Arm 2: BGB-10188 320 mg orally once daily + tislelizumab 200 mg intravenously once every 3 weeks

Ongoing safety and efficacy monitoring will be conducted. Safety and efficacy data will be reviewed by the SMC after approximately 12 patients have been randomized and followed for at least 1 month, or after the first 10 patients are evaluable for efficacy assessment. During the study, either arm that shows intolerable toxicity can be terminated, and additional lower dose(s) of BGB-10188 (eg, 80 mg orally once daily) may be added at any time. Study enrollment may be paused if there is a lack of efficacy during the interim review and may be reassumed if efficacy signal was observed with longer follow-up. The pause of enrollment and termination of either arm by the sponsor would be discussed and agreed by the SMC.

The study schema of Part E is presented in Figure 2.

Figure 2: Study Schema of Part E



Abbreviations: Bev, bevacizumab; CPI, checkpoint inhibitor; EOC, epithelial ovarian cancer; PARPi, PARP inhibitor; PROC, platinum-resistant ovarian cancer; Tisle, tislelizumab.

4. STUDY POPULATION

The specific eligibility criteria for selection of patients are provided in Section 4.1 and Section 4.2. The sponsor will not grant any eligibility waivers.

4.1. Inclusion Criteria

Each patient eligible to participate in this study must meet all the following criteria:

Part A, Part B, and Part C

1. Able to provide written informed consent and can understand and agree to comply with the requirements of the study and the schedule of assessments.
2. Age ≥ 18 years on the day of signing the informed consent form (ICF; or the legal age of consent in the jurisdiction in which the study is taking place).
3. Two negative pregnancy tests (≥ 1 blood test) must be obtained for female patients of childbearing potential prior to initiating therapy. The first test must be performed within 14 days prior to BGB-10188 therapy and the second test within 72 hours prior to first dose.
4. Confirmed diagnosis of one of the following:
   - Part A: R/R CLL/SLL, R/R MZL, R/R FL, R/R MCL, or R/R DLBCL
   - Part B and Part C: R/R FL, R/R MCL, or R/R DLBCL

   R/R disease is defined for patients who must have either: 1) disease progression after CR or PR of the last line of systemic therapy, or 2) failure to achieve CR or PR to the most recent appropriate systemic therapy. For the patients with CLL/SLL, the patient must experience relapsed or refractory disease from at least 1 cycle of systemic therapy, including BTK inhibitors or BCL-2 inhibitors, with or without CD20 monoclonal antibody-based chemotherapy, or must be intolerant to or refuse standard treatment. For the patients with B-cell NHLs, the patients must experience relapsed or refractory disease from at least 1 cycle of systemic therapy, such as immunomodulators, alkylating agents, or BTK inhibitors, with or without CD20 monoclonal antibody-based chemotherapy, or must be intolerant to or refuse standard treatment.
5. ECOG Performance Status of 0 to 1.
6. Patients with MZL, FL, MCL, DLBCL or SLL must have ≥ 1 bidimensionally measurable nodal lesion > 1.5 cm in the longest diameter or extranodal lesion that is > 1 cm in the longest diameter by CT scan or magnetic resonance imaging (MRI), as defined by the Lugano Classification.
7. Adequate organ function, defined as the following:
   a. Absolute neutrophil count (ANC) ≥ 1 x 10^9/L, independent of growth factor support within 7 days before the first dose of study drug
   b. Platelet count ≥ 75 x 10^9/L, independent of IL-11, thrombopoietin, or transfusion within 7 days before first dose of study drug; platelet count ≥ 50 x 10^9/L with bone marrow involvement

c. Hemoglobin > 90 g/L, independent of transfusion within 7 days before first dose of study drug
d. AST and ALT ≤ 2 x upper limit of normal (ULN)
e. Bilirubin ≤ 1.5 x ULN (unless documented Gilbert syndrome, then up to 5 x ULN allowed)
f. Creatinine clearance of ≥ 50 mL/min (as estimated by the Cockcroft-Gault equation or eGFR from the modification of diet in renal disease)
g. International normalized ratio (INR) ≤ 1.5 x ULN and activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN

8. Left ventricular ejection fraction > 50% as measured by echocardiogram or multigated acquisition scan.
9. Life expectancy of > 4 months.
10. Female patients of childbearing potential must practice highly effective methods of contraception (Appendix 7) initiated prior to first dose of study drug for the duration of the study and for ≥ 90 days after the last dose of BGB-10188 or zanubrutinib.
11. Male patients are eligible if abstinent, vasectomized, or if they agree to the use of barrier contraception with other methods described in Appendix 7 during the study treatment period and for ≥ 90 days after the last dose of BGB-10188 or zanubrutinib. Male patients must not donate sperm from the time of initial study drug administration, until 90 days after the last dose of BGB-10188 or zanubrutinib.

Part D

1. Able to provide written informed consent and can understand and agree to comply with the requirements of the study and the schedule of assessments.
2. Age ≥ 18 years on the day of signing the ICF (or the legal age of consent in the jurisdiction in which the study is taking place).
3. Two negative pregnancy tests must be obtained (≥ 1 blood test) for female patients of childbearing potential prior to initiating therapy. The first test must be performed within 14 days prior to BGB-10188 therapy and the second test within 72 hours prior first dose.
4. Patients with histologically or cytologically confirmed unresectable locally advanced or metastatic solid tumors previously treated with standard systemic therapy (including prior chemotherapy, radiotherapy, target therapy and immunotherapy as locally, or guidance approved therapy) or for which effective standard treatment is not available or not tolerated. Enrollment will be limited to patients with advanced solid tumors for which there is clinical evidence of response to T-cell based immuno-oncology agents (eg, NSCLC, small cell lung cancer, head and neck squamous cell cancer, hepatocellular carcinoma, gastric or gastroesophageal junction carcinoma, nasopharyngeal carcinoma, renal cell carcinoma, cervical cancer, triple-negative breast cancer, OC, endometrial carcinoma, esophageal cancer, melanoma, urothelial carcinoma, or patient with confirmed MSI-H or dMMR solid tumor, etc). Enrollment of tumor types beyond above situations requires sponsor's approval.

5. Availability of archival tissue (formalin-fixed paraffin-embedded [FFPE] tumor tissue sample [block or approximately 10 to 15 unstained FFPE slides]) for analysis of potential predictors of response expression, or willingness to undergo fresh tumor biopsy. A fresh tumor biopsy collected at screening is strongly recommended. If archival samples are not available or not sufficient enough for explorations, a fresh tumor biopsy collected at screening is required. Bone metastasis biopsy or cytological samples are not acceptable.
6. ECOG Performance Status of 0 to 1.
7. Patient must have ≥ 1 measurable lesion as defined by RECIST v1.1.
8. Adequate organ function, defined as the following:
    a. ANC ≥ 1.5 x 10^9/L, independent of growth factor support within 7 days
    b. Platelet count ≥ 75 x 10^9/L, independent of thrombopoietin, IL-11 or transfusion within 7 days
    c. Hemoglobin > 90 g/L, without blood transfusion ≥ 7 days before sample collection
    d. Creatinine clearance of ≥ 50 mL/min (as estimated by the Cockcroft-Gault equation or eGFR from the modification of diet in renal disease)
    e. Serum total bilirubin ≤ 1.5 x ULN (< 3 x ULN for patients with Gilbert syndrome)
    f. AST and ALT ≤ 2 x ULN for patients with liver metastasis ≤ 5 x ULN
    g. INR ≤ 1.5 x ULN and aPTT ≤ 1.5 x ULN
9. Female patients of childbearing potential must practice highly effective methods of contraception (Appendix 7) initiated prior to first dose of study drug for the duration of the study and for ≥ 90 days after the last dose of BGB-10188 or ≥ 120 days after the last dose of tislelizumab.
10. Male patients are eligible if abstinent, vasectomized, or if they agree to the use of barrier contraception with other methods described in Appendix 7 during the study treatment period and for ≥ 90 days after the last dose of BGB-10188 or ≥ 120 days after the last dose of tislelizumab.
11. Adequate pulmonary function, defined as the following:
    a. Without clinical symptoms of dyspnea at rest and pulse oxygen saturation > 92% while breathing room air, or
    b. Forced expiratory volume in one second (FEV1), forced vital capacity (FVC), carbon monoxide diffusion capacity (DLCO), or transfer factor for carbon monoxide of lung (TLCO) > 50% of predicted value, as well as FEV1/FVC > 60% as measured by pulmonary function test.

Part E

1. Patients must sign a written ICF and understand and agree to comply with the requirements of the study and the schedule of assessments.
2. Age ≥ 18 years on the day of signing the ICF (or the legal age of consent in the jurisdiction in which the study is taking place).
3. Patients with histologically or cytologically confirmed epithelial OC (including fallopian, or primary peritoneal cancer) and must meet the following criteria:

- Patients must have received ≥ 1 line and ≤ 3 lines of systemic anticancer treatment.
- Must be platinum resistant, which is defined if disease progression occurred between 1 month (30 days) to 6 months (180 days) after the last platinum treatment (disease progression within 1 month [≤30 days] after last platinum treatment is not acceptable).
- Patients must have a known Breast Cancer gene (BRCA) status and should have been treated with Poly (ADP-ribose) polymerase (PARP) inhibitors if there was BRCA mutation.

Note: A line of anticancer treatment starts when there is disease progression assessed by the investigator per local practice (eg, imaging, biopsy, CA-125). Maintenance treatment is not a new line of anticancer treatment. A line of anticancer treatment may be constituted with chemotherapy, Tyrosine kinase inhibitor (TKI), PARP inhibitors, or other anticancer agents.

4. Measurable disease as assessed by RECIST v1.1.
5. ECOG Performance Status ≤ 1.
6. Adequate organ function as indicated by the following laboratory values:
   a. Patients must not have required blood transfusion or growth factor support ≤ 14 days before sample collection at screening for the following:
      i. ANC ≥ 1.5 x 10^9/L
      ii. Platelets ≥ 75 x 10^9/L
      iii. Hemoglobin ≥ 90 g/L
   b. Estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration equation (Appendix 12).
   c. Serum total bilirubin ≤ 1.5 x ULN (total bilirubin must be < 5 x ULN for patients with Gilbert syndrome).
   d. AST and ALT ≤ 2 x ULN or < 5 x ULN if hepatic metastases are present.
7. Females of childbearing potential must be willing to use a highly effective method of birth control for the duration of the study and for ≥ 120 days after the last dose of tislelizumab. They must also have a negative urine or serum pregnancy test result ≤ 7 days before first dose of study drug. See Appendix 7.
8. Availability of archival tissue (FFPE tumor tissue sample [block or approximately 10 to 15 unstained FFPE slides]) for analysis of potential predictors of response expression, or willingness to undergo fresh tumor biopsy. A fresh tumor biopsy collected at screening is strongly recommended. If archival samples are not available or not sufficient enough for explorations, a fresh tumor biopsy collected at screening is required. Bone metastasis biopsy or cytological samples are not acceptable.

4.2. Exclusion Criteria

Patients who meet any of the following criteria are not eligible to enroll:

Part A, Part B, and Part C

1. History of allogeneic stem-cell transplantation or chimeric antigen receptor-T-cell therapy.
2. For patients with DLBCL in Part A, classified as T-cell/histiocyte-rich large B-cell lymphoma, high-grade B-cell lymphoma with myelocytomatosis viral oncogene homolog and B-cell lymphoma (BCL)-2 and/or BCL-6 rearrangements, high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, Epstein-Barr virus positive DLBCL, and transformed DLBCL.
3. Prior exposure to PI3K inhibitor (all patients). For patients in Part B and Part C, prior exposure to BTK inhibitor and/or PI3K inhibitor.
4. Major surgery within 4 weeks before screening.
5. History of other active malignancies within 2 years prior to study entry, with the exception of (1) adequately treated in situ carcinoma of cervix; (2) localized basal cell or squamous cell carcinoma of skin; (3) previous malignancy confined and treated locally (surgery or other modality) with curative intent.
6. Clinically significant cardiovascular disease including the following:
    a. Myocardial infarction within 6 months before screening
    b. Unstable angina within 3 months before screening
    c. Clinically significant ventricular arrhythmia (eg, sustained ventricular tachycardia, ventricular fibrillation, torsade de pointes)
    d. QTcF interval (Fridericia's correction) > 480 msec
    e. History of second-degree atrioventricular (AV) block type II or third-degree AV block without a permanent pacemaker in place.
    f. New York Heart Association (NYHA) class III or IV congestive heart failure (Appendix 8)
7. History of severe bleeding disorders, such as hemophilia A, hemophilia B, von Willebrand disease, or history of spontaneous bleeding requiring blood transfusion or other medical intervention.
8. History of stroke or intracranial hemorrhage within 6 months before first dose of study drug.
9. Unable to swallow capsules or having a disease significantly affecting gastrointestinal function such as malabsorption syndrome, resection of the stomach or small bowel, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.
10. Uncontrolled systemic infection requiring parenteral intravenous anti-infective therapy.
11. Known HIV infection, or serologic status reflecting active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection as follows:
    a. Hepatitis B surface antigen (HBsAg) (+), or
    b. Hepatitis B core antibody (HBcAb) (+) and HBV DNA detected, or
    c. Presence of HCV antibody. Patients with presence of HCV antibody are eligible if HCV RNA is undetectable.

12. Known hypersensitivity to compounds of similar chemical or biologic composition to PI3K inhibitor. For patients in Part B and Part C, known hypersensitivity to compounds of similar chemical or biologic composition to BTK inhibitor.
13. Pregnant or lactating women.
14. Any life-threatening illness, medical condition, or organ system dysfunction, which, in the investigator's opinion, could compromise the patient's safety or put the study at risk.
15. Requires ongoing treatment with strong and moderate CYP3A inhibitors or inducers (Appendix 10). If patients have been on a strong or moderate CYP3A inhibitors or inducers in the past, they will not be eligible if the administration was within 7 days before the first dose of study drug.
16. Concurrent participation in another therapeutic clinical study.
17. Current or history of CNS lymphoma.
18. Histologically confirmed transformed lymphoma.
19. Receipt of the following treatments prior to first dose of study drug:
    a. Corticosteroids (at doses > 20 mg/day prednisone equivalent) given with antineoplastic intent within 7 days
    b. Chemotherapy or radiotherapy within 5 half-lives or 14 days, whichever is shorter
    c. Monoclonal antibody within 5 half-lives or 14 days, whichever is shorter
    d. Investigational therapy within 5 half-lives or 14 days, whichever is shorter
    e. Chinese patent medicine with antineoplastic intent within 5 half-lives or 14 days, whichever is shorter
20. Toxicity of ≥ Grade 2 from prior anticancer therapy (except for alopecia, ANC, hemoglobin, and platelets. For ANC, hemoglobin, and platelets, please follow inclusion criterion #7 for Part A, Part B, and Part C).

Part D

1. Pleural effusion, pericardial effusion, or ascites that requires drainage procedures within 14 days before first dose.
2. Active leptomeningeal disease or uncontrolled brain metastasis. Patients with a history of treated and asymptomatic CNS metastases at screening are eligible per the following criteria:
    a. Brain imaging at screening shows no evidence of interim progression.
    b. All brain metastases with supratentorial location.
    c. No ongoing requirement for corticosteroids as therapy for CNS disease; anticonvulsant use at a stable dose is allowed.
    d. No stereotactic radiation or whole-brain radiation ≤ 14 days before the first dose of study drug(s).

3. Active autoimmune diseases or history of autoimmune diseases that may relapse or history of life-threatening toxicity related to prior immune therapy, with the following exceptions:
   a. Controlled type 1 diabetes
   b. Hypothyroidism (provided it is managed with hormone replacement therapy only)
   c. Controlled celiac disease
   d. Skin diseases not requiring systemic treatment (eg, vitiligo, psoriasis, or alopecia)
   e. Any other disease that is not expected to recur in the absence of external triggering factors
4. Prior exposure to PI3K inhibitor.
5. Any condition that required systemic treatment with either corticosteroids (> 10 mg daily of prednisone or equivalent) or other immunosuppressive medication ≤ 14 days before the first dose of BGB-10188, with the following exceptions:
   a. Adrenal replacement steroid (dose ≤ 10 mg daily of prednisone or equivalent).
   b. Topical, ocular, intra-articular, intranasal, or inhalational corticosteroid with minimal systemic absorption.
   c. Short course (≤ 7 days) of corticosteroid prescribed prophylactically (eg, for contrast dye allergy) or for the treatment of a nonautoimmune condition (eg, delayed-type hypersensitivity reaction caused by contact allergen).
6. History of interstitial lung disease, noninfectious pneumonitis, or uncontrolled lung diseases, including but not limited to pulmonary fibrosis, acute lung diseases, etc.
7. Uncontrolled diabetes or > Grade 1 laboratory test abnormalities in potassium, sodium, or corrected calcium despite standard medical management or ≥ Grade 3 hypoalbuminemia ≤ 14 days before the first dose of study drug(s).
8. Severe chronic or active infections (including but not limited to tuberculosis infection) requiring systemic treatment ≤ 14 days before the first dose of study drug(s).
   - Antiviral therapy is permitted for patients with hepatocellular carcinoma.
9. Known HIV infection, or serologic status reflecting active HBV or HCV infection as follows:
   a. HBsAg (+), or
   b. HBcAb (+) and HBV DNA detected, or
   c. Presence of HCV antibody. Patients with presence of HCV antibody are eligible if HCV RNA is undetectable.
10. Major surgical procedure, open biopsy, or significant traumatic injury ≤ 4 weeks before the first dose of study drug(s) or anticipation of need for major surgical procedure during the course of the study.
11. Prior immunodeficiency, allogeneic stem-cell transplantation, or organ transplantation.

12. Any of the following cardiovascular criteria:
    a. Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living, ≤ 28 days before the first dose of study drug(s)
    b. Symptomatic pulmonary embolism or other clinically significant episode of thromboembolic disease ≤ 28 days before the first dose of study drug(s)
    c. History of acute myocardial infarction ≤ 6 months before the first dose of study drug(s)
    d. History of heart failure meeting NYHA Classification III or IV (Appendix 8) ≤ 6 months before the first dose of study drug(s)
    e. Ventricular arrhythmia ≥ Grade 2 in severity ≤ 6 months before the first dose of study drug(s)
    f. Cerebrovascular accident ≤ 6 months before the first dose of study drug(s)
    g. QTcF interval (Fridericia's formula) > 480 msec
    h. Cardiac left ventricular ejection fraction ≤ 50% as measured by echocardiogram or multigated acquisition scan. The same modality used at baseline must be applied for subsequent evaluations.
    i. Uncontrolled hypertension: systolic pressure ≥ 160 mmHg or diastolic pressure ≥ 100 mmHg despite antihypertension medications ≤ 28 days before the first dose of study drug(s)
    j. Syncope or seizure ≤ 28 days before the first dose of study drug(s)
    k. History of second-degree AV block type II or third-degree AV block without a permanent pacemaker in place
13. Unable to swallow capsules or having a disease significantly affecting gastrointestinal function, such as malabsorption syndrome, resection of the stomach or small bowel, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.
14. Chemotherapy, immunotherapy (eg, interleukin, interferon, or thymosin), hormonal therapy, or investigational therapy ≤ 14 days or ≥ 5 half-lives (whichever is shorter) before the first dose of study drug(s)
15. Toxicities from prior therapy that have not recovered to baseline, ≤ Grade 1, or stabilized, except for AEs not considered a likely safety risk (eg, alopecia, neuropathy, and specific laboratory abnormalities)
16. Live vaccine ≤ 4 weeks before the first dose of study drug(s)
    - Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed.
17. Known hypersensitivity to compounds of similar chemical or biologic composition to PI3K inhibitor or to PD-1/PD-L1 antibodies.
18. Pregnant or lactating women.
19. Requires ongoing treatment with strong and moderate CYP3A inhibitors or inducers (Appendix 10). If patients have been on a strong or moderate CYP3A inhibitors or inducers in the past, they will not be eligible if the administration was within 7 days before the first dose of study drug.

20. Concurrent participation in another therapeutic clinical study.
21. Medical condition or alcohol or drug abuse or dependence that, in the investigator's opinion, will be unfavorable for the administration of study drug(s) or will affect the explanation of drug toxicity or AEs or are likely to result in insufficient compliance with study procedures.
22. History of other active malignancies within 2 years prior to study entry, with the exception of: (1) adequately treated in situ carcinoma of cervix; (2) localized basal cell or squamous cell carcinoma of skin; (3) previous malignancy confined and treated locally (surgery or other modality) with curative intent.

Part E

1. Prior exposure to PI3K inhibitor.
2. Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, or any other antibody or drug specifically targeting T-cell stimulation or checkpoint pathways.
3. COVID-19 antigen positive by a licensed test.
4. Prior randomization in a tislelizumab study regardless of the treatment arm, until the primary and key secondary endpoints of the study have read out.
5. Active leptomeningeal disease or uncontrolled, untreated brain metastasis.
   - Patients with a history of treated and, at the time of screening, stable CNS metastases are eligible, provided they meet all the following:
     - Brain imaging at screening shows no evidence of interim progression, and there is no evidence of new brain metastases.
     - Patient clinically stable for ≥ 2 weeks.
     - Have measurable and/or evaluable disease outside the CNS.
     - No ongoing requirement for corticosteroids as therapy for CNS disease; off steroids 3 days before randomization; anticonvulsants at a stable dose are allowed.
     - No stereotactic radiation or whole-brain radiation ≤ 14 days before randomization.
6. Active autoimmune diseases or history of autoimmune diseases that may relapse.

Note: Patients with the following diseases are not excluded and may proceed to further screening:

a. Controlled type 1 diabetes
b. Hypothyroidism (provided that it is managed with hormone replacement therapy only)
c. Celiac disease controlled by diet alone
d. Skin diseases not requiring systemic treatment (eg, vitiligo, psoriasis, alopecia)
e. Any other disease that is not expected to recur in the absence of external triggering factors

7. Any malignancy ≤ 5 years before first dose of study drug except for the specific cancer under investigation in this study and any locally recurring cancer that has been treated curatively (eg, resected basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix or breast).
8. Any condition that required systemic treatment with either corticosteroids (> 10 mg daily of prednisone or equivalent) or other immunosuppressive medication ≤ 14 days before first dose of study drug.

   Note: Patients who are currently or have previously been on any of the following steroid regimens are not excluded:

   a. Adrenal replacement steroid (dose ≤ 10 mg daily of prednisone or equivalent)
   b. Topical, ocular, intra-articular, intranasal, or inhaled corticosteroid with minimal systemic absorption
   c. Short course (≤ 7 days) of corticosteroid prescribed prophylactically (eg, for contrast dye allergy) or for the treatment of a nonautoimmune condition (eg, delayed-type hypersensitivity reaction caused by contact allergen
9. With uncontrolled diabetes or > Grade 1 laboratory test abnormalities in potassium, sodium, or corrected calcium despite standard medical management or ≥ Grade 3 hypoalbuminemia ≤ 14 days before first dose of study drug.
10. Uncontrollable pleural effusion, pericardial effusion, or ascites requiring frequent drainage (recurrence ≤ 14 days after intervention).
11. History of interstitial lung disease, noninfectious pneumonitis, or uncontrolled lung diseases including pulmonary fibrosis, or acute lung diseases. Patients with significantly impaired pulmonary function or who require supplemental oxygen at baseline must undergo an assessment of pulmonary function at screening (see Appendix 4).
12. Infection (including tuberculosis infection, etc) requiring systemic (oral or intravenous) antibacterial, antifungal, or antiviral therapy ≤ 14 days before first dose of study drug.

Note: Antiviral therapy is permitted for patients who have chronic infection with HBV, or infection with HIV. Patients receiving prophylactic antibiotics (eg, for prevention of urinary tract infection, chronic obstructive pulmonary disease, or for dental extraction) are eligible.

13. Untreated chronic hepatitis B or chronic HBV carriers with HBV DNA ≥ 500 IU/mL (or ≥ 2500 copies/mL) at screening.

Note: Inactive HBsAg carriers, treated and stable hepatitis B (HBV DNA < 500 IU/mL or < 2500 copies/mL) can be enrolled.

14. Patients with active hepatitis C

    Note: Patients with a negative HCV antibody test at screening or positive HCV antibody test followed by a negative HCV RNA test at screening are eligible.
15. Untreated HIV infection, if known. Patients with known HIV infection are eligible if the following criteria are met:

    a. Stable on antiretroviral therapy for ≥ 4 weeks before first dose of study drug
    b. Patient agrees to adhere to antiretroviral therapy per WHO guidelines

c. No documented multidrug resistance that would prevent effective antiretroviral therapy
d. Viral load of < 400 copies per mL at screening
e. CD4+ T-cell count ≥ 350 cells/μL at screening
f. No history of an AIDS-defining opportunistic infection ≤ 12 months before first dose of study drug unless eligibility is agreed to by the medical monitor after consultation
g. If prophylactic antimicrobial drugs are indicated, patients may still be eligible upon agreement with the medical monitor

16. Any major surgical procedure ≤ 28 days before first dose of study drug. Patients must have recovered adequately from the toxicity and/or complications from the intervention before first dose of study drug.
17. Prior allogeneic stem-cell transplantation or organ transplantation.
18. Any of the following cardiovascular risk factors:
    a. Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living, ≤ 28 days before first dose of study drug
    b. Pulmonary embolism ≤ 28 days before first dose of study drug
    c. Any history of acute myocardial infarction ≤ 6 months before first dose of study drug
    d. Any history of heart failure meeting NYHA Classification III or IV (Appendix 8) ≤ 6 months before first dose of study drug
    e. Any event of ventricular arrhythmia ≥ Grade 2 in severity ≤ 6 months before first dose of study drug
    f. Any history of cerebrovascular accident ≤ 6 months before first dose of study drug
    g. Uncontrolled hypertension that cannot be managed by standard antihypertension medications ≤ 28 days before first dose of study drug
    h. Any episode of syncope or seizure ≤ 28 days before first dose of study drug
19. A history of severe hypersensitivity reactions to other monoclonal antibodies.
20. Has received any chemotherapy, immunotherapy (eg, interleukin, interferon, thymosin, etc) or any investigational therapies ≤ 14 days or ≤ 5 half-lives (whichever is shorter) before the first dose of study drug, or has received palliative radiation treatment or other local regional therapies ≤ 14 days before the first dose of study drug.
21. Patients with toxicities (as a result of prior anticancer therapy) that have not recovered to baseline or stabilized, except for AEs not considered a likely safety risk (eg, alopecia, neuropathy, and specific laboratory abnormalities).
22. Was administered a live vaccine ≤ 28 days before first dose of study drug

Note: Vaccines for COVID-19 are allowed except for any live vaccine that may be developed. Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed.

23. Underlying medical conditions (including laboratory abnormalities) or alcohol or drug abuse or dependence that will be unfavorable for the administration of study drug, will affect the explanation of drug toxicity or AEs, or will result in insufficient or impaired compliance with study conduct.

24. Women who are pregnant or are breastfeeding.

25. Concurrent participation in another therapeutic clinical study.

Note: Concurrent participation in observational or noninterventional studies is allowed. In addition, patients who have completed active treatment in a clinical study and are in the follow-up period can be enrolled in this study.

26. Unable to swallow capsules or disease significantly affecting gastrointestinal function such as malabsorption syndrome, resection of the stomach or small bowel, bariatric surgery procedures, or symptomatic partial or complete bowel obstruction.

Note: Controlled partial bowel obstruction might be eligible.

27. Family history, medical history, or ongoing condition of inflammatory bowel disease (eg, Crohn's disease, ulcer colitis).

Note: Patients with other causes of diarrhea or colitis must be resolved for at least 7 days before first dose of study drug

28. Requires ongoing treatment with a strong or moderate CYP3A inhibitor or inducer (see Appendix 10). If patients have been on a strong or moderate CYP3A inhibitors or inducers in the past, they will not be eligible if the administration was within 7 days before the first dose of study drug.

29. QTcF interval (Fridericia's correction) > 450 ms.

Note: For any QTcF > 450 ms on initial ECG, a follow-up ECG will be performed in triplicate (ie, 3 separate ECGs recorded approximately 2 minutes apart). Patients with mean follow-up QTcF ≤ 450 ms are eligible.

5. STUDY TREATMENT

5.1. Study Treatment Preparation and Dispensation

5.1.1. BGB-10188

The full chemical name of BGB-10188 fumarate is 3-[(1*S*)-1-(8-amino-1-methylimidazo[1,5-*a*]pyrazin-3-yl)ethyl]-5-chloro-6-fluoro-*N*-[2-(4-methylpiperazin-1-yl)ethyl]-2-[(propan-2-yl)oxy]benzamide fumarate.

BGB-10188 fumarate is a white to light yellow powder with a molecular formula of $C_{30}H_{39}ClFN_7O_6$ and a molecular weight of 648.13 Daltons. BGB-10188 fumarate capsules are supplied in 20-mg and 80-mg strengths. Size 3 hydroxypropyl methylcellulose (HPMC) capsules are used for the 20-mg strength. Size 0 HPMC capsule shells are used for the 80-mg strength. Inactive ingredients include microcrystalline cellulose, mannitol, sodium starch glycolate, colloidal silicon dioxide, and magnesium stearate. All excipients are compendial. The product is supplied in high-density polyethylene (HDPE) bottles with desiccants.

The study drug must be kept at the temperature condition specified on the label.

The contents of the label will be in accordance with all applicable local regulatory requirements.

Refer to the Pharmacy Manual for details regarding administration, accountability, and disposal. Please also refer to the BGB-10188 IB for other details regarding BGB-10188.

5.1.2. Zanubrutinib

Zanubrutinib 80-mg capsules will be provided in HDPE bottles.

The study drug must be kept at the temperature condition specified on the label.

The contents of the label will be in accordance with all applicable local regulatory requirements.

Refer to the Pharmacy Manual for details regarding administration, accountability, and disposal. Please also refer to the zanubrutinib IB for other details regarding zanubrutinib.

5.1.3. Tislelizumab

Tislelizumab is a monoclonal antibody formulated for intravenous injection in a single-use vial (20R glass, US Pharmacopeia type I), containing a total of 100 mg of antibody in 10 mL of isotonic solution. Tislelizumab has been aseptically filled in single-use vials with a Flurotec-coated butyl rubber stopper and an aluminum cap. Each vial is packaged into a single-carton box.

The contents of the label will be in accordance with all applicable local regulatory requirements.

The study drug must be kept at the temperature condition as specified on the label.

Refer to the Pharmacy Manual for details regarding IV administration, accountability, and disposal. Please also refer to the tislelizumab IB for other details regarding tislelizumab.

5.2. Dosage and Administration

5.2.1. BGB-10188

BGB-10188 will be taken orally daily each morning with a glass of water (approximately 240 mL). Patients must be fasted for at least 2 hours before dosing and will remain fasted for 2 hours after dosing.

In Part A, 5 proposed dose levels will be tested: 60 mg once daily, 120 mg once daily, 240 mg once daily, 360 mg once daily, and 540 mg once daily. Additional dose levels may be added if deemed appropriate. In Part A only, all patients will receive a single dose of BGB-10188 followed by a washout period of 7 days.

In Part B, the initial oral, daily dose of BGB-10188 will start at the latest cleared dose of BGB-10188 monotherapy (Part A). Approximately 3 dose levels are planned to be tested for Part B. Dose levels may be changed or added as necessary based on the SMC review.

In Part D, the initial oral daily dose of BGB-10188 will start at 20 mg once daily. Approximately 6 proposed dose levels will be tested: 20 mg once daily, 40 mg once daily, 80 mg once daily, 160 mg once daily, 320 mg once daily, and 540 mg once daily. BGB-10188 should be given ≥ 30 minutes before tislelizumab infusion. Additional dose levels may be added if deemed appropriate.

In Part E, patients will be randomly assigned to receive either one of the 2 doses as starting dose: 160 mg once daily or 320 mg once daily. BGB-10188 will be taken orally daily each morning with a glass of water (approximately 240 mL). Patients must be fasted for at least 2 hours before dosing and will remain fasted for 2 hours after dosing. At Day 1 of each cycle, BGB-10188 should be given ≥ 30 minutes before tislelizumab infusion. Additional dose(s) of BGB-10188 (eg, 80 mg orally once daily) may be added during the study with the warrant and agreement by the SMC.

If 1 dose of BGB-10188 is missed, the patient will skip the missed dose and resume the same daily dose at the scheduled time on the next day. If 2 or more doses of BGB-10188 are missed, the patient should take 1 daily dose immediately after realizing the missed doses; the time of day when this make-up dose was taken (Restart Time) will become the new scheduled dosing time for the following days. Patients should continue to take the same daily dose at this new scheduled time on the next day.

5.2.2. Zanubrutinib

Zanubrutinib 160 mg will be administered orally twice a day. When taken in combination with BGB-10188, zanubrutinib will be taken following BGB-10188 dosing.

Zanubrutinib will be dispensed by the study center personnel to patients at scheduled study visits to ensure adequate drug supply for administration at home throughout the treatment phase as detailed in the Pharmacy Manual. The investigator is to instruct the patient to take the study drug exactly as prescribed and at the same time each day of dosing. Patients will be requested to bring their unused medication and all empty bottles to the center at each visit. All dosages prescribed and dispensed to the patient and all dose changes, including reason for dose changes during the study, must be recorded on the appropriate electronic case report form (eCRF).

Zanubrutinib will be administered as two 80-mg capsules by mouth twice daily (160 mg twice daily) with or without food. Patients will take zanubrutinib with water at approximately the same time every day with a minimum of 8 hours between consecutive doses. Zanubrutinib capsules should not be opened, broken, or chewed at any time.

Patients with disease progression in Part A can receive the cleared dose of BGB-10188 in combination with zanubrutinib at the investigator's discretion based on the local guidance and zanubrutinib prescribing information, which has been approved by local authorities that the patients can benefit from treatment in combination with zanubrutinib. This should be discussed and approved by the sponsor.

If a dose of zanubrutinib is missed, patients will be advised to take the same dose immediately after realizing the missed dose and return to the next regularly scheduled dose. However, if it is 4 hours or less to the next scheduled dose, patients should skip the missed dose, and the make-up dose is not recommended.

5.2.3. Tislelizumab

Tislelizumab 200 mg will be administered on Day 8 of Cycle 1 and Day 1 of each subsequent cycle in Part D and Day 1 of each cycle in Part E. In Part D, Cycle 1 is 28 days in length and all subsequent cycles are 21 days in length. In Part E, a cycle is defined as 21 days in length.

Tislelizumab will be administered by IV infusion through an IV line containing a sterile, nonpyrogenic, low-protein-binding 0.2 or 0.22 micron in-line or add-on filter. Specific instructions for product preparation and administration are provided in the Pharmacy Manual.

As a routine precaution, after infusion of tislelizumab on Day 8 of Cycle 1 (Part D)/Day 1 of Cycle 1 (Part E) and Day 1 of Cycle 2, patients must be monitored for ≥ 60 minutes afterward in an area with resuscitation equipment and emergency agents. From Cycle 3 onward, a ≥ 30-minute monitoring period is required in an area with resuscitation equipment and emergency agents.

The initial infusion (Cycle 1 Day 8 for Part D and Cycle 1 Day 1 for Part E) will be delivered over 60 minutes; if this is well tolerated, then the subsequent infusions may be administered over 30 minutes, which is the shortest period permissible for infusion. Tislelizumab must not be concurrently administered with any other drug (refer to Section 6).

Guidelines for dose modification, treatment interruption, or discontinuation and for the management of imAEs and IRRs are provided in detail in Section 5.5, Section 8.7, and Appendix 9.

Refer to the Pharmacy Manual for detailed instructions on drug preparation, storage, and administration.

5.3. Compliance and Accountability

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or guardian.

The investigator and/or study personnel will keep accurate records of the quantities of study drug dispensed and used by each patient. This information must be captured in the source document at each patient visit. The investigator is responsible for study drug accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the investigator or designated study center personnel must maintain study drug accountability records throughout the course of the study. This person will document the amount of study drug received from the sponsor, the amount supplied, and/or administered to and returned by patients, if applicable.

5.4. Overdose

Any dose of BGB-10188 or zanubrutinib in excess of that specified in this protocol or of tislelizumab ≥ 600 mg in a 24-hour period is considered to be an overdose. Incorrect administration of study drug should be noted in the patient's chart and on the appropriate eCRF AEs associated with an overdose of study drug will be recorded on the AE eCRF. Any SAEs associated with an overdose are required to be reported within 24 hours of awareness via SAE reporting process as described in Section 8.6. There is no specific antidote for BGB-10188, zanubrutinib, or tislelizumab overdose. In the event of an overdose, patients should be closely monitored and given appropriate supportive treatment.

5.5. Dose Hold or Modification

Every effort should be made to administer the study drug(s) according to the planned dose and schedule. In the event of significant toxicities, dosing may be held and/or reduced based on the guidelines provided below. Reasons for dose modifications or holds, the supportive measures taken, and the outcome will be documented in the patient's chart and recorded in the eCRF.

5.5.1. BGB-10188

5.5.1.1. Dose Escalation

Patients on lower dose levels who have a suboptimal response, as determined by the investigator following disease assessment, may be allowed to increase their dose to higher dose levels that have subsequently been declared tolerable. This must be approved by the sponsor. Once the RDFE is identified, the dose for patients on lower doses may be increased to the RDFE at the investigator's discretion using a plan approved by the SMC. Any significant safety events that occur in these patients (eg, events that meet the definition of a DLT) will be reviewed by the SMC for evaluating the safety of the doses.

Dose interruption of BGB-10188 will be allowed for DLT and other reasons. Dose interruption because of a DLT event is allowed in DLT observation window. Dosing of BGB-10188 can be withheld for up to 28 consecutive days.

Dose reduction of BGB-10188 for the management of AEs will be allowed beyond the DLT observation window (28 days from C1D1 and up to 8 weeks prolonged window). The AEs should be unlikely related to zanubrutinib in Part B or tislelizumab in Part D, or the relatedness is uncertain. This dose reduction must be determined by the investigator following disease assessment and approved by the sponsor. The dose can be reduced to the one prior cleared dose that is confirmed by SMC. A total maximum of 2 dose reductions will be allowed throughout

the whole treatment period. For patients with AEs not recovered or worsened from the first dose reduction, the patients will be strongly recommended to have dose interruption or discontinue from the treatment.

Dose interruptions that lead to a drug compliance rate less than 75% of the prescribed dosage during the DLT assessment period, and for reasons other than DLT, will cause the patient to be replaced (Section 3.2.3). After the DLT assessment period, if in the investigator's opinion, it is in the patient's best interest to restart treatment after dose interruptions > 28 days, written approval must be obtained from the sponsor's medical monitor.

For patients in Parts A and B who experience diarrhea and colitis, atypical infection such as *pneumocystis jirovecii pneumonia* (PJP), or cytomegalovirus (CMV) infection after the DLT window, the guidelines set forth should be followed (Table 1). For Grade 1 to 2 rash, BGB-10188 treatment can be maintained but should be interrupted for Grade 3 rash while managing and treating rash per institutional guidelines. For Grade 3 rash, BGB-10188 can be resumed at a reduced dose (-1 dose) if resolved to baseline. For pneumonitis, BGB-10188 treatment can be maintained for Grade 1 and should be interrupted for Grade 2; patients experiencing Grade 3 pneumonitis should discontinue BGB-10188. Treatment for pneumonitis should be manage and provided according to institutional guidelines.

Table 1: Guidelines for Dose Modifications of BGB-10188 in Part A and B

Event	Action for BGB-10188
Grade 1 Diarrhea OR Grade 1 Colitis	Maintain study treatment Manage and initiate treatment per institutional guidelines Monitor approximately weekly until resolved
Grade 2 Diarrhea	Interrupt study treatment until resolved Manage and initiate treatment per institutional guidelines Resume at a reduced dose (-1 dose) if resolved to baseline
Grade 3 Diarrhea OR Grade 2-3 Colitis	Interrupt study treatment until resolved Manage and initiate treatment per institutional guidelines Monitor closely until resolved Resume at a reduced dose (-1 dose) if resolved to baseline For recurrent Grade 3 diarrhea or recurrent colitis of ≥ Grade 2, discontinue study treatment
Grade 4 Diarrhea OR Grade 4 Colitis	Discontinue study treatment Manage and initiate treatment per institutional guidelines
Grade 1-2 Rash	Maintain study treatment Manage and initiate treatment per institutional guidelines
Grade 3 Rash	Interrupt study treatment until resolved Manage and initiate treatment per institutional guidelines Resume at a reduced dose (-1 dose) if resolved to baseline

Grade 4 Rash	Discontinue study treatment Manage and initiate treatment per institutional guidelines
Pneumocystis jirovecii pneumonia Any grade	Discontinue BGB-10188.
CMV infection/reactivation Any grade	Interrupt BGB-10188 upon unequivocal clinical or laboratory evidence of CMV infection and initiate treatment according to established clinical guidelines. If the benefits of resuming BGB-10188 are judged to outweigh the risks, consideration should be given to administering prophylactic CMV therapy.

5.5.1.2. Dose Expansion (Part E)

In Part E, patients will be randomly assigned to receive either 320 or 160 mg dose levels of BGB-10188 as starting dose. The treatment of BGB-10188 may be temporally withheld or reduced if the patient experiences a toxicity that is suspected to be related to BGB-10188. Treatment may resume only after the AEs have returned to baseline or ≤ Grade 1 severity or AEs that, in the opinion of the investigator, are not considered a safety risk to the patient. The decision of treatment resumption should be applied to both BGB-10188 and tislelizumab if dose modification was previously applied to both study drugs. For reasons other than drug-related AEs, eg, safety concerns due to the poor health condition, if deemed necessary by the investigators, dose modifications could be applied after discussion with medical monitor.

Dosing of BGB-10188 can be withheld for up to 28 consecutive days to allow for resolution of toxicity. If additional dose interruptions are required, the treating investigator should discuss with the study medical monitor. A maximum of 2 dose reductions are permitted (Table 2). Once the dose has been decreased, it should remain reduced for all subsequent administrations or further reduced if necessary. There will be no dose escalations in this study.

If the decision of study drug discontinuation is made, the decision should be applied to both BGB-10188 and tislelizumab. If a patient is benefiting from the study treatment while meeting the discontinuation criteria, resumption of study treatment may occur upon discussion and agreement with the medical monitor, the decision of resumption should be applied to both BGB-10188 and tislelizumab.

Dose modification guidance for AEs that have been previously observed in subjects receiving BGB-10188 or are potential class-effect AEs is provided in Table 3. Dose modification guidance for diarrhea/colitis is provided in Section 5.6. Dose modification guidance for other AEs is provided in Table 4.

Table 2: BGB-10188 Dose Reduction Levels in Part E

Timepoint	Dose Level	Dose Level
Starting dose	160 mg	320 mg
First dose reduction	120 mg	240 mg
Second dose reduction	80 mg	160 mg

Table 3: Guidelines for Dose Modifications of BGB-10188 in Part E

Adverse Reactions	Severity	Dose Modification
Hematologic Adverse Reactions		
Neutropenia	ANC 0.5 to 1.0 x 10^9/L (Grade 3)	Interrupt BGB-10188 until ANC resolved to > 1.0 x 10^9/L (Grade 2), then resume at same dose.
	ANC < 0.5 x 10^9/L (Grade 4)	Interrupt BGB-10188 until ANC resolved to > 1.0 x 10^9/L (Grade 2), then resume at same dose. If recurrence or persistent for > 7 days, interrupt BGB-10188 until ANC resolved to > 1.0 x 10^9/L (Grade 2), then resume at next lower dose level.
Thrombocytopenia	Platelet count 25 to 50 x 10^9/L (Grade 3)	Interrupt BGB-10188 until platelet count resolved to > 50 x 10^9/L (Grade 2), then resume at same dose.
	Platelet count < 25 x 10^9/L (Grade 4) or any grade platelet count decrease with bleeding not explained by alternative causes	Interrupt BGB-10188 until platelet count resolved to > 50 x 10^9/L (Grade 2), then resume at same dose. If recurrence or persistent for > 7 days, interrupt BGB-10188 until platelet count resolved to > 50 x 10^9/L (Grade 2), then resume at next lower dose level.
Nonhematologic Adverse Reactions		
ALT/AST elevation	ALT/AST 3 to 5 x ULN (Grade 2)	Maintain BGB-10188. If recurrence or persistent for > 14 days, interrupt BGB-10188 until ALT/AST resolved to < 3 x ULN (Grade 1), then resume at same dose.
	ALT/AST 5 to 20 x ULN (Grade 3)	Interrupt BGB-10188 until ALT/AST resolved to < 3 x ULN (Grade 1), then resume at same dose. If recurrence or persistent for > 14 days, interrupt BGB-10188 until ALT/AST resolved to < 3 x ULN (Grade 1), then resume at next lower dose level.
	ALT/AST > 20 x ULN (Grade 4)	Discontinue BGB-10188.
Cutaneous reactions (eg, rash, pruritus)	Grade 2	Maintain BGB-10188. If recurrence or persistent for > 14 days, interrupt BGB-10188 until resolved to ≤ Grade 1, then resume at same dose.

Adverse Reactions	Severity	Dose Modification
	Grade 3	Interrupt BGB-10188 until resolved to ≤ Grade 1, then resume at next lower dose level.
	Grade 4	Discontinue BGB-10188.
Pneumonitis	Grade 1	Interrupt BGB-10188 until resolved then resume at same dose. If recurrence, interrupt BGB-10188 until resolved then resume at next lower dose level.
	Grade 2	Interrupt BGB-10188 until resolved then resume at next lower dose level. If recurrence or patient does not respond to steroid therapy, discontinue BGB-10188
	Grade 3 or 4	Discontinue BGB-10188.
Infections	Grade 3	Interrupt BGB-10188 until resolved then resume at next lower dose level.
	Grade 4	Discontinue BGB-10188.
Note: • ≥ Grade 3 laboratory findings (ANC, platelet count, ALT/AST) should be frequently monitored (at least weekly) until resolved to ≤ Grade 1. • For patients with liver metastasis or abnormal baseline ALT/AST, please contact sponsor to discuss dose modifications.		

Abbreviations: ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; ULN, upper limit of normal.

Table 4: Guidelines for Dose Modifications of BGB-10188 Regarding AEs not Mentioned in Table 3 in Part E

Adverse Reactions	Dose Modifications
Grade 1 or Grade 2 toxicity	Continue BGB-10188 and treat the toxicity; increase the monitoring frequency as clinically indicated.
Grade 3 toxicity	Step 1: Interrupt BGB-10188 up to 28 days until the toxicity is resolved to ≤ Grade 1. Step 2: Resume BGB-10188 at same dose or reduce 1 dose level
Recurrent Grade 3 toxicity after 2 dose reductions	Interrupt BGB-10188 up to 28 days until the toxicity is resolved to ≤ Grade 1 and resume at same dose, or discontinue BGB-10188.
Grade 4 toxicity	Discontinue BGB-10188.

5.5.2. Zanubrutinib

In Part B (combination of BGB-10188 and zanubrutinib), patients experiencing a DLT should be considered for permanent treatment discontinuation following the dose escalation rule for BGB-10188. However, such patients may continue to receive additional zanubrutinib if clinically appropriate in the judgment of the investigator and after consultation with and approval by the medical monitor.

The guidelines set forth should be followed for dose interruption or modification of zanubrutinib for hematologic (Section 5.5.2.1) or nonhematologic (other than hypertension adequately controlled with oral medication or asymptomatic laboratory events; laboratory events indicating liver or renal dysfunction will not be considered asymptomatic laboratory events) (Section 5.5.2.2) toxicities after the DLT window.

Table 5: Zanubrutinib Dose Reduction Levels

Toxicity Occurrence	Dose Level	Zanubrutinib Dose
First	0 = starting dose	Restart at 160 mg twice daily [a]
Second	-1 dose level	Restart at 80 mg twice daily
Third	-2 dose level	Restart at 80 mg once daily
Fourth	Discontinue zanubrutinib	Discontinue zanubrutinib

Abbreviations: DLT, dose-limiting toxicity.

[a] During the DLT period in Cycle 1, patients are not eligible to restart at 160 mg twice daily and must reduce dose to the -1 dose level after the first DLT. After the second DLT, patients must reduce dose to the -2 dose level. After the third DLT, patients must discontinue zanubrutinib.

Zanubrutinib may be restarted upon resolution of toxicity and per investigator discretion if held for a maximum of 28 consecutive days. If, in the investigator's opinion, it is in the patient's best interest to restart treatment after > 28 days, then written approval must be obtained from the sponsor's medical monitor.

5.5.2.1. Zanubrutinib Dose Reductions for Hematologic Toxicity

Dosing will be held for individual patients under any of the following conditions, based on investigator assessment of study-drug relatedness:

- Grade 4 neutropenia (lasting > 10 days)
- Grade 4 thrombocytopenia (lasting > 10 days)
- Grade 3 thrombocytopenia associated with significant bleeding
- ≥ Grade 3 febrile neutropenia

For the first occurrence of hematologic toxicity, treatment may restart at full dose upon recovery of the toxicity to ≤ Grade 1 or baseline.

If the same event reoccurs, patients will restart at 1 dose level lower upon recovery of the toxicity to ≤ Grade 1 or baseline. A maximum of 2 dose reductions will be allowed. Patients with ≥ Grade 3 thrombocytopenia associated with significant bleeding requiring medical intervention will be discussed with the medical monitor.

5.5.2.2. Zanubrutinib Dose Reductions for Nonhematologic Toxicity

Table 6: Zanubrutinib Dose Reduction Steps for Nonhematologic Toxicity

Toxicity	Action for Zanubrutinib	Restart Dose
≥ Grade 3 hemorrhage not considered related to study drug	Hold until recovery to less than or equal to Grade 1.	Restart at either the original dose or dose level (-1), at the discretion of the treating investigator.
≥ Grade 3 hemorrhage considered related to study drug	Hold until underlying condition has fully resolved. If underlying condition cannot be treated to full resolution, permanently discontinue zanubrutinib.	Restart at dose level (-1).
Any grade intracranial hemorrhage	Permanently discontinue zanubrutinib.	Not applicable
AF that is symptomatic and/or incompletely controlled	Hold until AF is controlled.	Restart at either the original dose or dose level (-1), at the discretion of the treating investigator.
Other ≥ Grade 3 toxicity considered related to study drug, including inadequately controlled HTN and/or liver or renal laboratory value abnormalities	Hold until recovery to less than or equal to BL if BL is greater than Grade 1; hold until less than or equal to Grade 1 if BL is less than or equal to Grade 1.	Restart at the original dose level.

Abbreviations: AF, atrial fibrillation; BL, baseline; HTN, hypertension.

Zanubrutinib should be withheld for any ≥ Grade 3 hemorrhage. The drug should be permanently discontinued for any related ≥ Grade 3 hemorrhage with the exception of those where the underlying condition can be fully treated (eg, gastric ulcer resulting in gastrointestinal bleed) and the risk of a re-bleed is deemed acceptable. Zanubrutinib should be permanently discontinued for any intracranial hemorrhage.

For nonhematological toxicities ≥ Grade 3, other than hypertension adequately controlled with oral medication or asymptomatic laboratory events (laboratory events indicating liver or renal dysfunction will not be considered asymptomatic laboratory events) suspected to be related to study drug treatment, study drug will be held until recovery to ≤ Grade 1 or baseline, and then restarted at original dose level. If the event recurs at ≥ Grade 3, drug will be held until recovery to ≤ Grade 1 or baseline and restarted at level -1. If the event recurs at ≥ Grade 3, drug will be held until recovery to ≤ Grade 1 and restarted at level -2. If the event recurs at ≥ Grade 3 at level -2, the patient will be discontinued from study treatment. For patients experiencing atrial fibrillation that is symptomatic and/or incompletely controlled: after the atrial fibrillation is adequately controlled, zanubrutinib may be restarted at either the original dose or dose level -1, per discretion of the treating investigator.

For information on study drug holds based on the results of hepatitis B or hepatitis C testing, see Section 7.5.7.

5.5.3. Tislelizumab

There will be no dose reduction for tislelizumab in this study.

Patients may temporarily suspend study treatment if they experience toxicity that is considered related to tislelizumab and requires a dose to be withheld. If the administration delay is ≤ 10 days, the delayed drug will be administered; if the delay is > 10 days, the delayed drug will be omitted in this cycle, and the next cycle will be administered as planned as long as the AE resolves within 21 days.

The patients should resume tislelizumab treatment as soon as possible after the AEs recover to baseline or Grade 1 (whichever is more severe) and within 12 weeks after the last dose of tislelizumab. If the patient is unable to resume tislelizumab within 12 weeks after the last dose of tislelizumab, then the patient should be discontinued from treatment.

If a patient is benefiting from the study treatment while meeting the discontinuation criteria, resumption of study treatment may occur upon discussion and agreement with the medical monitor.

Dose modifications for imAEs and IRRs are described in Appendix 9 and Section 8.7.1, respectively.

5.6. Management Guidelines for Treatment-Related Diarrhea or Colitis (Part E)

Subjects should inform the investigator immediately on any event of diarrhea. In all incidences, development of diarrhea while using BGB-10188 should be evaluated urgently with close follow-up until improvement.

Subjects presenting with diarrhea, a thorough history, physical examination and necessary laboratory testing should be performed during the initial patient examination (Table 7). For each occurrence, attempts should be made to rule out other causes, such as metastatic disease or viral infection, which might require additional supportive care. Diagnostic colonoscopy is recommended for atypical cases (eg, bloody diarrhea) or those in whom the recommended treatment interventions do not lead to resolution of diarrhea.

For subjects with any-grade diarrhea, dietary modification is instructed (Table 8). Solid foods can be gradually added after diarrhea is improved.

Note: When treatment-related diarrhea is suspected, the causality judgment should be carefully assessed. If there is strong evidence suggesting diarrhea is only related to tislelizumab, the diarrhea should be managed according to the guidance provided in Appendix 9. In other situations, the dose modification guideline is provided in Table 9. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased.

Table 7: Evaluation and Diagnostic Testing Recommendations for Subjects Presenting Diarrhea

History and Physical Examination	Laboratory Testing
Physical examination, including assessment of fever, dizziness, abdominal pain/cramping, and weakness History of onset and duration of diarrhea Travel history Description of number of stools and stool composition (eg, watery, bloody, nocturnal) Medication profile to identify diarrheagenic agents Dietary profile to identify diarrheagenic foods	Stool work-up Occult blood determination Culture for enteric pathogens (*Salmonella*, *Escherichia coli*, *Campylobacter*, infectious colitis) *Clostridium difficile* CBC, electrolytes, and BUN/Cr Consider colonoscopy in selected cases

Source: Coutré et al 2015
Abbreviations: BUN, blood urea nitrogen; CBC, complete blood count; Cr, creatinine.

Table 8: Diet Modification Recommendations for Subjects With Diarrhea

Diet Modifications
Drink plenty of fluids, 8 to 12 glasses a day of oral-rehydration drinks, other clear liquids or clear broth to replace lost fluids and minerals.
Eat 5 to 6 small meals each day.
Eat low-fat, high-protein foods, such as lean meat and eggs.
Try BRAT (bananas, rice, apple sauce, toast) diet to help lessen the number of bowel movements.
Try crackers, gelatin, noodles, or oatmeal.
Eat cooked instead of raw vegetables, and remove skins from fruits before eating.
Avoid fried, fatty, greasy, or spicy foods.
Avoid milk (if it makes the diarrhea worse), milk products (including ice cream), and acidic drinks (eg, tomato juice, citrus juices, fizzy soft drinks).
Avoid foods that cause gas (eg, broccoli and cabbage) and high-fiber foods.
Avoid caffeine, alcohol, and herbal supplements (some may cause diarrhea).

Source: American Cancer Society 2013; National Cancer Institute 2012

Table 9: Management and Dose Modification Guidance for Treatment-Related Diarrhea/Colitis

Grade 1	Maintain BGB-10188 and tislelizumab. Treat with antimotility agents (eg, 4 mg loperamide followed by 2 mg every 4 hours or after every unformed stool). Monitor approximately every 48 hours. If improved within 48 hours, continue dietary modification, and gradually add in solid foods; discontinue loperamide after 12-hour symptom-free interval. If not improved after 48 hours, treat per guidance for Grade 2.
Grade 2	Interrupt BGB-10188 and delay tislelizumab.

	Complete evaluation for infection (eg, CMV, C. *difficile*) immediately. Monitor approximately every 48 hours. If improved to ≤ Grade 1 within 48 hours and/or infection is confirmed, resume BGB-10188 and tislelizumab at same dose (for infectious diarrhea/colitis, follow institutional standard-of-care, or consult with medical monitor if needed). If not improved to ≤ Grade 1 after 48 hours and infection is ruled out, start oral budesonide 9 mg once daily or oral steroid (eg, prednisolone 1 mg/kg daily), or consider IV steroids if patient is being given IV fluids. If no improvement with oral steroid, switch to IV steroids. When diarrhea/colitis is resolved to ≤ Grade 1 after steroid treatment, taper steroids according to institutional standard-of-care. When taper is completed (≤ 10 mg/day prednisone or equivalent), resume BGB-10188 at next lower dose and resume tislelizumab. If Grade 2 reoccurs, treat per guidance for Grade 2 again. If Grade 2 reoccurs a third time, discontinue BGB-10188 and tislelizumab.
Grade 3	For the first occurrence, treat per guidance for Grade 2. If Grade 3 reoccurs, discontinue BGB-10188 and tislelizumab.
Grade 4	Discontinue BGB-10188 and tislelizumab.

Source: Hanlon and Brander 2020; Kryvenko 2015
Abbreviations: CMV, cytomegalovirus; IV, intravenous.

5.7. Precautions

Phototoxicity

Because the molar extinction coefficient greater than 1000 L mol^{-1} cm^{-1} was noted in ultraviolet A between 320 and 347 nm, a potential phototoxicity risk in skin is considered. Investigators should advise patients to take measures, such as avoid direct sunlight and use UV protection, eg, use of sunscreen and wearing of hats and long-sleeve garments, to minimize exposure to UV light for the duration of the treatments.

6. CONCOMITANT THERAPY

6.1. Concomitant Therapy

All concomitant medications taken during the study will be recorded in the eCRF with indication and dates of administration.

Prophylactic measures against infection, for the prevention of bacterial or fungal infections and/or for the prevention of hepatitis B infection reactivation, should be used per institutional standards.

6.1.1. Permitted Concomitant Medications/Procedures

Most concomitant medications and therapies deemed necessary and in keeping with local standards of medical care at the discretion of the investigator for supportive care (eg, anti-emetics, antidiarrheals) and in a patient's interest are allowed.

6.1.1.1. Part A, Part B, and Part C

The following treatments are allowed:

- Blood transfusions and growth factor support per standard of care and institutional guidelines
- Corticosteroids for non-lymphoma indications
    - Patients should not receive treatment with systemic corticosteroids other than intermittently to control or prevent infusion reactions, or for short durations (< 14 days) to treat non-lymphoma-related conditions (eg, to treat a flare of chronic obstructive pulmonary disease).
    - A short course (≤ 7 days) of systemic corticosteroid treatment for control of lymphoma-related symptoms is allowed prior to enrollment provided it is tapered off within 5 days after initiation of study treatment.
    - Chronic systemic corticosteroid use is not permitted, except for adrenal replacement consult the medical monitor for this situation.
- Therapy to reduce symptoms per standard of care and institutional guidelines

Tumor lysis syndrome has not been currently reported with zanubrutinib treatment; however, it remains a concern. Patients with high tumor burden should be monitored closely and prophylactic measures, including allopurinol and hydration, may be instituted per institutional standards.

Patients with hematologic malignancies, particularly those having received prior lymphodepleting chemotherapy or having prolonged corticosteroid exposure, are predisposed to opportunistic infections as a result of disease and treatment-related factors. In patients with a high risk for opportunistic infections prophylaxis should be considered as per institutional standards. Patients must receive trimethoprim-sulfamethoxazole or other established prophylaxis for PJP throughout the course of BGB-10188 treatment. Prophylaxis will continue for a period of 2 to 6 months after BGB-10188 discontinuation. The duration of prophylaxis should be based

on clinical judgment and may take into account risk factors such as concomitant corticosteroid treatment and prolonged neutropenia after BGB-10188 treatment ends. Patients must permanently discontinue BGB-10188 upon diagnosis of PJP.

6.1.1.2. Part D and Part E

Unless noted otherwise, most concomitant medications and therapies deemed necessary and in keeping with local standards of medical care at the discretion of the investigator for supportive care (eg, anti-emetics, antidiarrheals, hematopoietic growth factors, or red blood cell/platelet transfusions) and in a patient's interest are allowed. Prophylactic drugs for PJP for patients with high risk should be considered.

All concomitant medications, including all prescription and over-the-counter drugs, supplements, and intravenous medications and fluids, taken by or administered to the patient within 28 days before the first dose of study drug(s) and 30 days after the last dose of study drug(s) will be recorded.

Bisphosphonates and RANKL inhibitors are allowed for bone metastases if initiated before enrollment and at a stable dose. Bisphosphonates are permitted during the study for a non-malignant indication.

Systemic corticosteroids given for the control of imAEs must be tapered gradually (see Appendix 9) and be at nonimmunosuppressive doses (≤ 10 mg/day of prednisone or equivalent) before the next tislelizumab administration. The short-term use of steroids as prophylactic treatments (eg, patients with contrast allergies to diagnostic imaging contrast dyes) is permitted.

Palliative (limited-field) radiation therapy is permitted for solid tumors, but only for pain control or prophylaxis of bone fracture to sites of bone disease present at baseline provided the following criteria are met:

- Repeat imaging demonstrates no new sites of bone metastases.
- The lesion being considered for palliative radiation is not a target lesion for RECIST v1.1.
- The case is discussed with the medical monitor, and the medical monitor agrees that the conditions required to receive palliative radiation are met.

Additionally, palliative radiation or other focally ablative therapy for other nontarget sites of the disease is permitted if clinically indicated per investigators' discretion and after consultation with the medical monitor. Whenever possible, these patients should have a tumor assessment of the lesion(s) before receiving the radiotherapy in order to rule out progression of disease.

It is not required to withhold BGB-10188 and/or tislelizumab treatment during palliative radiotherapy.

6.1.2. Prohibited Concomitant Medications/Procedures

The following medications are prohibited during the study:

- Live vaccines ≤ 28 days before first dose of study drugs and ≤ 60 days after the last dose of study drugs are prohibited.
- Any concurrent systemic anticancer therapy, including chemotherapy, hormonal therapy, immunotherapy, standard anticancer agents, or investigational anticancer agents are prohibited during screening and through the End-of-Treatment (EOT) Visit.
- BGB-10188 is CYP3A and P-gp substrates. Co-administration with strong CYP3A inhibitors or inducers and grapefruit juice and Seville oranges should be avoided. Please refer to Section 6.2 for more details.

6.1.3. Restricted Concomitant Medications/Procedures

The following medications are restricted during the study:

- Immunosuppressive agents (except to treat a drug-related AE).
- Patients should not abuse alcohol or other drugs during the study.
- Use of potentially hepatotoxic drugs in patients with impaired hepatic function should be carefully monitored.
- Radiation therapy is not allowed, except for palliative radiation therapy described in Section 6.1.1.
- Herbal remedies for the treatment of cancer or Chinese patent medicines with approval from the China NMPA for use as anticancer treatment (regardless of cancer type).
- Herbal remedies with immune-stimulating properties (eg, mistletoe extract) or that are known to potentially interfere with liver or other major organ functions (eg, hypericin).
- Co-administration with moderate CYP3A inhibitors or inducers should be done with caution (Appendix 10).

Opiates and other medication required for palliative management of patients are allowed. Patients must notify the investigator of all concurrent medications used during the study.

6.2. Potential Interactions Between the Study Drugs and Concomitant Medications

BGB-10188 and zanubrutinib are CYP3A and P-gp substrates. Co-administration with strong CYP3A inhibitors or inducers (see Appendix 10 for list of common inhibitors and inducers) and grapefruit juice and Seville oranges should be avoided. Co-administration with moderate CYP3A inhibitors or inducers should be done with caution, as they may affect the metabolism of BGB-10188 and zanubrutinib. If at all possible, patients are encouraged to not use strong/moderate CYP3A inhibitors and inducers and consider using alternative agents. If these agents will be used, follow the dose-modification table in Appendix 11 for zanubrutinib. Please refer to the FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers List (FDA 2019) for a more complete list.

Zanubrutinib is a mild inducer of CYP3A4 and CYP2C19. 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. Since blood levels and efficacy of drugs that are substrates for CYP3A (eg, steroidal contraceptives) may be reduced by CYP3A inducers, if patients are using hormonal contraceptives, such as birth control pills or devices, a second barrier method of contraception (eg, condoms) is recommended to be used. The coadministration of oral P-gp substrates with a narrow therapeutic index (eg, digoxin) should be used with caution as zanubrutinib may increase their concentrations.

The drug-drug interaction potential between tislelizumab and other small or large therapeutic molecules is low, given tislelizumab is a monoclonal antibody with no effect on drug metabolizing enzymes or transporters.

The medical monitor and clinical pharmacologist should be consulted for uncertain cases.

7. ENROLLMENT AND STUDY PROCEDURES

The scheduled study assessments are provided in Appendices (from Appendix 1 to Appendix 4). Patients will be closely monitored for safety and tolerability throughout the study. All assessments must be performed and documented in the medical record for each patient.

Dosing will occur only if the clinical assessment and local laboratory test values (which must be available before any dosing) have been reviewed and found to be acceptable per protocol guidelines.

7.1. Screening Period

Screening evaluations will be performed within 28 days prior to the first dose of study drug. In Part A, the first dose of drug will occur on Day -7 of Cycle 1 for PK studies. In Part B through Part E, the first dose of study drug will occur on Cycle 1 Day 1. Patients who agree to participate in this study will sign the ICF prior to undergoing any screening procedure. The screening period begins on the date the ICF is signed. Screening evaluations may be repeated as needed within the screening period; the investigator is to assess preliminary patient eligibility according to the latest screening assessment results.

Results of standard of care tests or examinations performed prior to obtaining informed consent and within 28 days prior to the first dose of study drugs (or window indicated) may be used for the purposes of screening rather than repeating the standard of care tests unless otherwise indicated.

For Part E, patients suspected of having or known to have concurrent serious respiratory illness or who exhibit significant respiratory symptoms unrelated to underlying cancer should undergo pulmonary function testing during screening or whenever clinically indicated (see Appendix 4).

Rescreening under limited conditions may be allowed after consultation with the sponsor. For example, rescreening may be considered when a patient narrowly misses a laboratory criterion that is correctable and not due to rapidly deteriorating condition or disease progression. Rescreening is allowed only once.

7.1.1. Informed Consent and Screening Log

Voluntary, written informed consent for participation in the study must be obtained before performing any study-specific procedures. ICFs for enrolled patients and for patients who are screened but not enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before first dose of study drugs. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

7.1.2. Demographics

Demographic factors such as age, gender, race, and ethnicity could influence the effects (safety and efficacy) of medicines and the risk/benefit assessment in different populations. Race and ethnicity data are collected in accordance with ICH guidance (ICH E5 1998, ICH E17 2017) adopted by the European Medicines Agency (EMA) and US FDA, to understand whether

race/ethnicity could influence the PK, safety, and/or efficacy of the study drug. For example, population PK analysis is a well-established, quantitative method that can quantify and explain the variability in drug concentrations among patients. Such variability can be attributed to intrinsic factors (eg, body weight, age, gender, race/ethnicity), or to extrinsic factors (eg, concomitant medications), and can lead to clinically relevant changes in drug concentrations that require a change in the dose or dosing regimen. Results from race/ethnicity and other demographic analyses will be incorporated into drug product labeling to provide guidance on safety and efficacy variations (if any) linked to certain populations (eg, race or ethnic group) as well as any potential dose adjustment needed for those populations. Therefore, collecting race/ethnicity data in the study is essential to understand whether race/ethnicity could influence the PK, safety, and/or efficacy.

7.1.3. Patient Numbering

After obtaining informed consent, study site personnel access the Interactive Response Technology (IRT) system to assign a unique patient number to a potential study participant. Patients who are rescreened will be assigned a new patient number. Screening numbers that are assigned to the same patient within the IRT system will be linked.

7.2. Enrollment

Prior to enrollment, the investigator is responsible for assessing and confirming that each patient meets all inclusion eligibility criteria for this study and that none of the exclusion criteria apply. All results from the screening procedures and relevant medical history must be available and reviewed by the investigator before eligibility can be determined. No eligibility waivers will be granted.

Sponsor verification of patient eligibility will be managed by way of source data verification in accordance with ICH E6.

The sponsor's medical monitor will support the investigator and/or site staff by answering any queries or questions relating to protocol eligibility criteria.

7.2.1. Randomization (Part E)

Study site personnel will access the IRT system to randomly assign the patient to a treatment arm and to assign study drug. Study treatment must commence ≤ 2 business days after randomization/treatment assignment.

7.3. Treatment Period

In Parts A, B, and C, a cycle is defined as 28 days in length. In Part D, Cycle 1 is 28 days in length and all subsequent cycles are 21 days in length. In Part E, a cycle is defined as 21 days in length.

BGB-10188 will be administered orally, once daily until unequivocal progression, unacceptable toxicity, death, withdrawal of consent, lost to follow-up, end of study, investigator's decision, or the study is terminated by sponsor, whichever comes first. The decision to receive BGB-10188 in combination with zanubrutinib beyond progression in Part A must be agreed upon with the medical monitor and documented in the study records.

Zanubrutinib 160 mg will be administered orally, twice daily until disease progression, unacceptable toxicity, death, withdrawal of consent, lost to follow-up, end of study, investigator's decision, or the study is terminated by sponsor, whichever comes first.

Tislelizumab 200 mg will be administered intravenously on Day 8 of Cycle 1 and Day 1 of each subsequent cycle in Part D and on Day 1 of each cycle in Part E until disease progression, unacceptable toxicity, death, withdrawal of consent, lost to follow-up, end of study, investigator's decision, or the study is terminated by sponsor, whichever comes first. The decision to continue tislelizumab beyond the initial investigator-assessed progression must be agreed upon with the medical monitor and documented in the study records.

BGB-10188 should be taken ≥ 30 minutes before tislelizumab infusion for patients in Part D and Part E.

Refer to Section 7.6 and Section 8.7 for additional considerations regarding treatment continuation and withdrawal.

7.3.1. Treatment Period (Part E)

For Part E, after completing all screening activities, eligible patients will be randomized in a 2:1 ratio to receive either BGB-10188 160 mg + tislelizumab 200 mg (Arm 1) or BGB-10188 320 mg + tislelizumab 200 mg (Arm 2).

Patients will receive open-label treatment with one of the following:

- Arm 1: BGB-10188 160 mg orally once daily + Tislelizumab 200 mg intravenously once every 3 weeks
- Arm 2: BGB-10188 320 mg orally once daily + Tislelizumab 200 mg intravenously once every 3 weeks

Ongoing safety monitoring will be conducted for enrolled patients. With emerging clinical evidence, the arm that shows intolerable toxicity could be terminated at any time by sponsor and upon the agreement by the SMC. Additional dose(s) of BGB-10188 (eg, 80 mg orally once daily) may be added during the study.

Administration of study drugs will continue until disease progression is assessed by the investigator per RECIST v1.1 (Section 7.6), unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met (whichever occurs first; see Section 7.13).

In both arms, treatment beyond the initial investigator-assessed RECIST v1.1-defined disease progression is permitted provided that the patient has investigator-assessed clinical benefit and is tolerating study drug (Section 7.6.2).

7.4. Visit Windows

All visits must occur within ± 3 days of the scheduled date, unless otherwise noted (from Appendix 1 to Appendix 4). All assessments will be performed on the day of the specified visit unless an acceptable time window is specified. Assessments scheduled on the day of study treatment administration (Day 1 of each cycle) should be performed before study drug administration unless otherwise noted. Laboratory results should also be reviewed before study drug administration.

In Parts A, B, and C, the study visit schedule is based around 28-day cycles. Procedures for a given visit may be split across the window to allow for drug resupply and completion of study procedures.

In Parts D and E, the study visit schedule is based around 21-day cycles except for Part D Cycle 1, which is based around a 28-day schedule. In Part D, all cycles after Cycle 1 will be calculated every 3 weeks starting from Cycle 1 Day 8. If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other event, the visit should be scheduled on the nearest feasible date, with subsequent visits conducted according to the planned schedule every 3 weeks from Day 1 of Cycle 2 (Part D) or Day 1 of Cycle 1 (Part E).

7.5. Safety Assessments

7.5.1. Physical Examination and Vital Signs

A complete physical examination that includes an assessment of cardiovascular, respiratory, abdominal, and neurological systems as well as lymph nodes/spleen, skin, oropharynx, and extremities will be performed at screening. A targeted examination should be limited to systems of clinical relevance (ie, cardiovascular, respiratory, lymph nodes, liver, and spleen), and those systems associated with clinical signs/symptoms will be performed at PK washout and at each visit. Vital signs (sitting blood pressure, pulse rate, and body temperature) will be performed after the patient has rested in the sitting position for ≥ 3 minutes at screening, at PK washout, at each visit during study treatment, at EOT, and at the Safety Follow-up Visit. Weight will be assessed at screening and at every visit as indicated in the Schedule of Assessments. Height (cm) is determined at screening only. B-symptoms, which include unexplained weight loss > 10% over the previous 6 months, fever (> 38°C), and/or drenching night sweats will be assessed for patients in Parts A, B, and C only.

Assessment of vital signs and a targeted physical examination on Cycle 1 Day 1 may be skipped if performed within the last 7 days.

7.5.2. Ophthalmologic Examination (Part D)

Because immune CPIs like tislelizumab may be associated with imAEs involving the eye, an eye examination, including 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 first dose of study drug 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 (see Appendix 9).

7.5.3. Eastern Cooperative Oncology Group Performance Status

ECOG Performance Status (Appendix 16) will be assessed per the Schedules of Assessment.

7.5.4. Laboratory Safety Tests

Laboratory assessments of serum chemistry, hematology, coagulation, urinalysis, and thyroid function will be conducted, of which certain elements will be collected per the timepoints specified in Appendix 1 through Appendix 4.

Details about sample collection and shipment will be provided in a separate instruction manual.

Laboratory Assessments

Chemistry, CBC, coagulation, urinalysis, serum immunoglobins, thyroid function (Part D and Part E), and hepatitis serologies will be performed at the timepoints specified in the Schedule of Assessments and may also be performed as medically necessary. In Cycle 1, laboratory assessments should be performed before the first dose of study drug.

Screening tests (including CBC, chemistry, and coagulation) performed within 72 hours before the first study drug administration do not need to be repeated in Cycle 1. Results of blood tests taken within 72 hours may be used by the investigators to make the decision to proceed with dosing. After Day 1 of Cycle 1, results are to be reviewed within 48 hours before study drug administration. Screening hepatitis serologies performed within 4 weeks before the first study drug administration do not need to be repeated in Cycle 1.

Urinalysis

Urinalysis, which includes pH, ketones, specific gravity, bilirubin, protein, blood, and glucose, will be performed at specified timepoints in the Schedule of Assessment.

Hematology

Hematology assessments (which include hemoglobin, hematocrit, platelets, red blood cells, WBCs, neutrophils, lymphocytes, monocytes, eosinophils, and basophils) are required to be performed as specified in the Schedule of Assessments.

Chemistry

Chemistry assessments include sodium, potassium, chloride, urea or blood urea nitrogen, creatinine, glucose, calcium, total protein, albumin, AST, ALT, ALP, total bilirubin, lactate dehydrogenase, phosphate or phosphorus, uric acid, magnesium, and bicarbonate. For patients in Part D and Part E, serum amylase and serum lipase will be performed at screening and as clinically indicated.

Chemistry assessments will be performed as specified per the Schedule of Assessments.

Coagulation Profile

The coagulation profile includes prothrombin time (which will also be reported as INR) and activated partial thromboplastin time. The coagulation profile will be performed as specified in the Schedule of Assessments.

Pregnancy Test

Two negative pregnancy tests must be obtained for all women of childbearing potential before initiation of therapy. The first test must be performed ≤ 14 days before BGB-10188 therapy and the second test ≤ 72 hours before BGB-10188 therapy. At least 1 test should be a blood pregnancy test.

Pregnancy testing will be performed as specified in the Schedule of Assessments. If a urine pregnancy test is positive, the result must be confirmed by a serum pregnancy test. A patient who has a positive pregnancy test result at any time after the study drug administration will be immediately withdrawn from participation in the study.

Thyroid Function Test (Part D and Part E)

Thyroid function testing includes thyroid stimulating hormone, free triiodothyronine [T3], and free thyroxine [T4].

7.5.5. Electrocardiograms

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper or electronic copies of ECG tracings will be kept as part of the patient's permanent study file at the study site.

All ECGs are to be obtained prior to other assessments scheduled at that same time. If this is not possible, then ECGs are to be obtained ≥ 20 minutes following the last procedure performed. The patient should rest in a supine position for ≥ 10 minutes in the absence of environmental distractions that may induce changes in heart rate (eg, television, radio, conversation, etc) before each ECG collection.

At each timepoint (see Appendix 5), 3 consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine the mean QTcF interval.

7.5.6. Adverse Events

AEs will be graded and recorded throughout the study according to NCI-CTCAE, v5.0 (NCI-CTCAE 2017). Characterization of toxicities will include severity, duration, and time to onset.

All AEs, including SAEs, will be collected as described in Section 8.6.

7.5.7. Hepatitis B and C Testing

7.5.7.1. Part A, Part B, Part C, and Part D

Hepatitis B and C serologic markers and/or viral load will be tested at screening. Hepatitis B and C testing must be conducted in a laboratory able to perform the test to the required sensitivity (< 20 IU/mL and < 15 IU/mL for hepatitis B and C, respectively). If sites cannot conduct the tests with this sensitivity or the results are not reported with values, then any positive viral load result should lead to withholding of study treatment and initiation of antiviral treatment. The hepatitis B testing includes HBsAg and HbcAb, as well as HBV DNA by polymerase chain reaction (PCR) if the patient is HbcAb positive (HbsAg negative). The hepatitis C testing includes HCV antibody as well as HCV RNA by PCR if the patient is HCV antibody positive. Patients with positive HbsAg and/or detectable level of HBV DNA or detectable level of HCV RNA are not eligible.

Patients who are HbcAb positive (HbsAg negative) and HBV DNA negative must undergo at least monthly HBV DNA screening by PCR (same for patients who are HbsAb positive who have not received the hepatitis B vaccine and are HbsAg negative). These patients should be

considered for prophylactic antiviral treatment in consultation with a local HBV expert. If a patient is being treated prophylactically with antivirals, HBV DNA screening by PCR must be done at least every 90 days.

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 14 days. Study drug should be held, and antiviral therapy initiated if the repeat level is between 20 IU/mL and 100 IU/mL. If the HBV DNA by PCR is 100 IU/mL or higher, then study drug should be held, and antiviral therapy initiated or continued. For patients whose HBV reactivation resolves, resumption of study drug should be discussed with, and approved by, the medical monitor and physicians with expertise in managing hepatitis B.

Patients positive for HCV antibody, but negative for HCV RNA, must undergo monthly HCV RNA screening. Patients with HCV RNA of 15 IU/mL or greater should stop study drug and antiviral therapy should be initiated. For patients whose HCV reactivation resolves, resumption of study drug should be discussed with, and approved by, the medical monitor and physicians with expertise in managing hepatitis C.

The medical monitor should be informed of any suspected hepatitis B or hepatitis C reactivation.

Table 10 and Table 11 describes how the results for HBV and HCV testing at screening relate to study eligibility.

Table 10: Hepatitis B Eligibility Criteria

HbsAg-Positive	HbcAb	HBV DNA	Eligible
Yes	Any	N/A	Not Eligible
No	Yes	Detected	Not Eligible
No	Yes	Undetected	Eligible [a]
No	No	N/A	Eligible [b]

Abbreviations: HbcAb, hepatitis B core antibody; HbsAg, hepatitis B surface antigen; HBV, hepatitis B virus; N/A, not applicable.
[a] Eligible if patient agrees to monthly monitoring of HBV DNA (or at least every 90 days for patients receiving prophylactic antiviral therapy).
[b] If patient is negative for HbsAg antibody and HbcAb, do not need HBV DNA test at screening.

Table 11: Hepatitis C Eligibility Criteria

HCV Antibody	HCV RNA	Eligible
Yes	Undetected	Eligible [a]
No	N/A	Eligible [b]
Yes	Detected	Not Eligible

Abbreviations: HCV, hepatitis C virus; N/A, not applicable.
[a] Eligible if patient agrees to monthly monitoring of HCV RNA.
[b] If patient is negative for HCV antibody, do not need HCV RNA test at screening.

7.5.7.2. Part E

Hepatitis B and C virus serologic markers and viral load will be tested by the local laboratory. HBV testing will include HbsAb, HbsAg, and HbcAb. In addition, HBV DNA will be quantified in patients positive for HbsAg. HCV testing will consist of HCV antibody plus HCV RNA in patients positive for HCV antibody.

7.5.8. Cardiac Enzyme Monitoring (Part D and Part E)

Although immune-mediated myocarditis is a rare complication of immune CPIs, serum creatine kinase (CK) and CK cardiac isoenzyme (CK-MB) is monitored in all tislelizumab studies to protect study participants and to quantify the risk of muscle inflammation. Testing of CK-MB will be performed by a central and/or the local laboratory at the timepoints specified in Appendix 3 and Appendix 4. If the site's laboratory does not perform CK-MB testing, serum troponins (troponin I and/or T) measurements should be performed instead; if only 1 of the troponins is assessed per local standards, that same test should be evaluated throughout.

If significant abnormalities are detected, the affected patients should be evaluated for possible myocarditis/myositis per institutional guidelines, including additional serum CK/CK-MB, serum troponin levels, ECG, etc. Report all clinically significant abnormalities as an AE or SAE.

7.5.9. Cytomegalovirus Monitoring

Patients will be monitored for CMV reactivation using quantitative PCR assay for CMV DNA according to Appendix 1 through Appendix 4. CMV surveillance for active disease (quantitative PCR or PP65 antigen) must be conducted approximately every cycle throughout the course of BGB-10188 treatment. CMV viral load testing should be performed from the same specimen type whenever possible, and caution should be exercised when comparing CMV viral load results across different testing centers. If unequivocal clinical or laboratory evidence of CMV infection is present, the patient must interrupt BGB-10188 treatment and undergo effective antiviral treatment according to established clinical guidelines. If the benefits of resuming BGB-10188 are judged to outweigh the risks, consideration should be given to administering prophylactic CMV therapy.

7.6. Tumor and Response Evaluations

Part A, Part B, and Part C

Response will be assessed and categorized per Lugano Classification for patients with NHL (including SLL, MZL, MCL, DLBCL, and FL) (Cheson et al 2014; Appendix 13). For patients with CLL, disease response will be determined in accordance with the 2018 iwCLL guidelines (Hallek et al 2018) with modification for treatment-related lymphocytosis (Cheson et al 2012) (Appendix 14). Response parameters will include CT scans and bone marrow aspirate/biopsy (in patients who experience a CR and who also had lymphoma bone marrow involvement at baseline). For patients with gastrointestinal involvement who had an endoscopy performed during the screening period, a follow-up endoscopy is required to confirm CR. In the event of a treatment delay, disease assessments are to continue per the Schedule of Assessments (Appendix 1).

Positron Emission Tomography/Computed Tomography

Patients with NHL (ie, MZL, MCL, FL, or DLBCL) will undergo PET/CT imaging at baseline; a separate CT scan of diagnostic quality should be performed in addition to the PET/CT imaging if the PET/CT imaging is not of diagnostic quality. If PET-avid disease is detected, then subsequent tumor assessments should be conducted with PET/CT-based imaging. Patients with NHL without PET-avid disease, as well as patients with CLL/SLL, should undergo tumor assessments with CT-based imaging.

CT with contrast of chest, abdomen, pelvis, and neck, will be performed at screening and while on study until disease progression, start of new anticancer therapy, withdrawal of consent, death, lost to follow-up, or end of study, whichever occurs first. Patients with disease progression in Part A who received the treatment of BGB-10188 in combination of zanubrutinib will continue all study assessments. 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, adheres to the specified slice thickness/scan parameters, and IV contrast is administered. Otherwise, both scans should be done.

All efforts will be made to ensure that the imaging equipment, contrast agent, and person (investigator or radiologist) performing the evaluation are kept constant throughout a patient's course on study.

An MRI may be used in place of CT only for patients who have a contraindication to CT scans. If used, MRI should be performed of neck, abdomen, pelvis, and any other disease sites. In addition to the MRI, a non-contrast CT of the chest should be performed.

Bone Marrow Examination

Bone marrow biopsy (for patients with CLL) and/or aspirate (for patients with NHL) is required during the screening period to assess bone marrow involvement of lymphoma or leukemia. If a patient has had bone marrow examination performed within 90 days prior to Cycle 1 Day 1, a repeated bone marrow biopsy/aspirate is not required.

Patients with baseline marrow involvement who meet clinical and laboratory criteria for CR or CR with incomplete bone marrow recovery (CRi) (CLL only) are required to have a bone marrow examination to confirm CR or CRi. This should be performed within 40 days from the CT/MRI meeting the criteria of CR or CRi. All the other clinical data should be collected within ± 14 days from the CT/MRI (ie, CBC with differential and physical examination). For patients with DLBCL, if a follow-up biopsy cannot be obtained, a PET scan that clearly documents continued disease clearance may be used in lieu of the repeated biopsy.

Part D and Part E

Tumor imaging will be performed within 28 days before the first dose of study drug. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and ≤ 28 days prior to first dose may be used for the purposes of screening rather than repeating the standard-of-care tests. During the study, tumor imaging will be performed at Week 10 (Part D, Appendix 3) or Week 9 (Part E, Appendix 4) and approximately every 9 weeks (± 7 days) thereafter, based on RECIST v1.1, until unequivocal progression, use of alternative anticancer therapy, withdrawal of consent, death, lost to follow-up, or end of study, whichever occurs first.

Screening assessments and each subsequent assessment of the tumor must include the CT scans (with oral/IV contrast, unless contraindicated) or MRI of the chest, abdomen, and pelvis. Other known or suspected sites of disease must be included in the imaging assessments (neck, brain, etc).

All measurable and evaluable lesions should be assessed and documented at the Screening Visit and reassessed at each subsequent tumor evaluation. The same radiographic procedure used to assess disease sites at screening are required to be used throughout the study (eg, the same contrast protocol for CT scans).

- Imaging of the brain (preferably MRI or CT) should be performed at screening only when clinically indicated and followed throughout the study, if there is evidence of metastatic disease in these regions at screening. Screening evaluations will be performed within 28 days prior to the first dose
- If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the study, a non-contrast CT of the chest plus a contrast-enhanced MRI (if possible) of abdomen and pelvis should be performed.
- If a CT scan for tumor assessment is performed on a PET/CT scanner, the CT acquisition must be consistent with the standards of a diagnostic CT scan.
- Bone scans (Technetium-99m [TC-99m]) or PET should be performed at screening if clinically indicated. If bone metastases are present at screening and cannot be seen on CT or MRI scans, TC-99m or PET bone scans should be repeated when a CR is suspected in target lesion or when progression in bone is suspected.
- CT scans of the neck or extremities should be performed at screening only if clinically indicated and followed throughout the study, if there is evidence of metastatic disease in these regions at screening.
- At the investigator's discretion, other methods of assessment of target lesion and nontarget lesions per RECIST v1.1 may be used.

Response will be assessed by the investigator using RECIST v1.1 (Appendix 17). The same evaluator should perform assessments, if possible, to ensure internal consistency across visits.

After first documentation of response (CR or PR), confirmation of tumor response should occur at 4 weeks or later, after the first response or at the next scheduled assessment timepoint.

7.6.1. Treatment After Disease Progression (Part A)

Patients with disease progression in Part A can continue the treatment of BGB-10188 at the cleared dose in combination with zanubrutinib if the patient is receiving clinical benefit at the investigator's discretion based on the local guidance and zanubrutinib prescribing information that has been approved by local authorities with prior approval from the medical monitor and additional patient consent. This is particularly encouraged for patients with disease indications aligned with the zanubrutinib market authorization in the respective country. Patients who receive the treatment of BGB-10188 in combination with zanubrutinib are required to complete all subsequent study assessments as listed in Appendix 1 before Part A reaches the end of study as defined in Section 7.14.

7.6.2. Treatment After Primary Progression of Disease (Part D and Part E)

Some patients may benefit from additional immune therapies despite evidence of disease progression. These patients may go on to exhibit a response at a later timepoint. It is the responsibility of the investigator to determine if the patient should be considered for treatment beyond progression due to clinical benefit. This decision should be considered carefully so as to permit patients who are likely to be benefiting to continue treatment while at the same time preventing prolonged exposure of a futile therapy to patients who may not be benefiting. Any decisions to continue treatment beyond initial progression must be discussed with the medical monitor and documented in the study records.

After the initial documentation of disease progression, a confirmation of tumor imaging will be performed ≥ 4 weeks after the tumor imaging that initially suggested the suspected progression. Patients with confirmed evidence of disease progression will discontinue from study drug, as specified in Section 7.13.1.

The following criteria must be met in order to treat patients with suspected evidence of disease progression:

- Absence of clinical symptoms and signs of disease progression (including clinically significantly worsening of laboratory values).
- Continuing to receive clinical benefit.
- Stable ECOG Performance Status ≤ 1.
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, cord compression) that requires urgent alternative medical intervention.
- Investigators must obtain written informed consent for treatment beyond radiologic disease progression and inform patients that this practice is not considered standard in the treatment of cancer.
- The decision to continue study drug(s) beyond initial investigator-assessed progression must be agreed upon with the medical monitor and documented in the study records.

Tumor assessments are required to be performed on schedule regardless of whether study treatment has been administered or held.

7.6.3. CA-125 Tumor Evaluations (Part E)

For Part E, CA-125 will be tested in a local laboratory within 14 days before the first dose of study drug, at Week 9, and then every 9 weeks (±7 days) thereafter until loss of clinical benefit, use of alternative anticancer therapy, withdrawal of consent, death, lost to follow-up, or end of study, whichever occurs first. Patients can be evaluated according to CA-125 only if they have a pretreatment sample that is at least twice the upper limit of the reference range and within 2 weeks before starting the treatment. When there is an initial CA-125 response, it is suggested to confirm the response after 28 days (+7 days) after the initial response.

7.7. Pharmacokinetic and Antidrug Antibody Testing

Part A, Part B, and Part C

Blood samples will be collected to characterize the PK profiles of specified compounds. All blood sampling for PK assessment will be collected at the timepoints specified in the Schedule of Assessments (Appendix 5). The actual collection date and time of each blood sample will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional timepoints upon sponsor approval to ensure thorough PK monitoring.

Shipping, storage, and handling of samples will be managed through a central laboratory. The plasma concentrations of specified testing articles will be tested using validated assays. Full details on sample collection, processing, storage, and shipment will be provided in the laboratory manual.

BGB-10188 PK Characterization

Serial plasma samples for BGB-10188 PK assessment will be collected during the PK washout period (only for Part A) and/or treatment Cycle 1 for all patients enrolled in dose escalation phases (see the full details in Appendix 5).

Sparse plasma samples for BGB-10188 PK assessment will be collected for the patients in expansion cohorts (see the full details in Appendix 5).

The sampling schedules for the combination escalation cohorts in Part B are subject to modification based on the preliminary data from the monotherapy escalation phase in Part A.

Zanubrutinib PK Characterization

For the zanubrutinib PK assessment, serial plasma samples will be collected from all patients in the combination escalation cohorts (Appendix 5).

Part D and Part E

Blood samples will be collected to characterize the PK profile and evaluate the antidrug antibody (ADA) for specified compounds. All blood sampling (plasma or serum) for PK assessment and ADA testing will be collected at the timepoints specified in the Schedule of Assessments (Appendix 5, Appendix 6). The actual collection date and time of each blood sample will be recorded. The timing of PK and ADA samples may be altered and/or PK and ADA samples may be obtained at additional timepoints upon sponsor approval to ensure thorough PK and ADA monitoring.

Shipping, storage, and handling of samples will be managed through a central laboratory. The plasma or serum concentrations of specified testing articles will be tested using validated assays. Full details on sample collection, processing, storage, and shipment will be provided in the laboratory manual.

BGB-10188 PK Characterization

Serial plasma samples for BGB-10188 PK assessment will be collected during treatment Cycles 1 and 2 from all patients enrolled in dose escalation phases in Part D, and approximately 5 patients (approximately 2 to 3 patients in each dose level) who were treated beyond C2D1 in Part E (see the full details in Appendix 5).

Sparse plasma samples for BGB-10188 PK assessment will be collected from the patients in Part E (see the full details in Appendix 5).

Blood will be collected to characterize the PK of BGB-10188 using a validated liquid chromatography-tandem mass spectrometry method.

Blood sampling for PK will be collected at the timepoints specified in the Schedule of Assessments (see Appendix 3 and Appendix 4). The samples will be sent to the sponsor or designee for storage and/or analysis.

Refer to the laboratory manual for instructions regarding sample collection, handling, labeling, storage, and shipping of laboratory samples to the central laboratory.

The sampling schedules for Part D and Part E are subject to modification based on the preliminary data from Part A.

Tislelizumab ADA and PK Characterization

In Part D and Part E, sparse blood samples will be collected at specified cycles for all patients in order to evaluate anti-tislelizumab-antibody and paired tislelizumab PK (see Appendix 6).

Tislelizumab may elicit an immune response. Patients with signs of any potential immune response to tislelizumab will be closely monitored. Validated screening and confirmatory assays will be employed to detect ADAs at multiple timepoints throughout the study (see Appendix 6). The immunogenicity evaluation will utilize a risk-based immunogenicity strategy (Koren et al 2008; Rosenberg and Worobec 2004a; Rosenberg and Worobec 2004b) to characterize ADA responses to tislelizumab in support of the clinical development program. This tiered strategy will include an assessment of whether ADA responses correlate with relevant clinical endpoints. Implementation of ADA characterization assays will depend on the safety profile and clinical immunogenicity data.

The following assessments will be performed at a central laboratory:

- ADA assays: serum samples will be tested for the presence of ADAs to tislelizumab using a validated immunoassay
- PK assay: serum samples will be assayed for tislelizumab concentration with the use of a validated immunoassay

Shipping, storage, and handling of samples for the assessment of tislelizumab PK and ADA assays will be managed through a central laboratory. Instruction manuals and supply kits will be provided for all central laboratory assessments.

7.8. Pharmacodynamics

Part A, Part B, and Part C

For patients enrolled in Part A and Part B, and the first 5 patients in Part C, phospho-AKT expression in blood samples will be determined and used as a direct pharmacodynamic biomarker for PI3Kδ inhibition. Blood immune cells will also be assessed to monitor pharmacodynamic changes after treatment with BGB-10188 monotherapy or in combination with zanubrutinib. Blood samples will be collected as stated in Appendix 5. The timing of pharmacodynamic samples may be altered upon sponsor approval to ensure sample collection at most relevant timepoints for pharmacodynamics study. Full details regarding sample collection, processing, storage, and shipment will be provided in the laboratory manual.

Part D and Part E

For patients enrolled in Part D and approximately 5 patients (approximately 2 to 3 patients in each dose level) in Part E, phospho-AKT expression in blood samples will be determined and used as a direct pharmacodynamic biomarker for PI3Kδ inhibition. Blood immune cells will also be assessed to monitor pharmacodynamic changes after treatment with BGB-10188 monotherapy or in combination with tislelizumab. Blood samples will be collected as stated in Appendix 5. The timing of pharmacodynamic samples may be altered upon sponsor approval to ensure sample collection at the most relevant timepoints for pharmacodynamics study. Full details on sample collection, processing, storage, and shipment will be provided in the laboratory manual.

7.9. Biomarkers

Tissue and blood samples for biomarker assessment will be collected as stated in Appendix 1 through Appendix 4. Shipping, storage, and handling of blood, archival tumor, fresh tumor, and leftover tumor tissue for the assessment of biomarkers will be managed through a central laboratory. Refer to the laboratory manual for details of sample handling.

Part A, Part B, and Part C

If available, either an FFPE block with tumor tissue (preferred) or 10 to 15 unstained slides should be sent to the central laboratory for analysis of potential predictors of response including assessment of PI3Kδ expression, Ki67 index, TP53 mutation status, presence of immune cells in the tumor microenvironment, genetic profiling, etc. If archival samples are not available then an optional, fresh tumor biopsy, to be collected at screening, will be requested. At the sites in mainland China, tissue will be obtained to assess PI3Kδ expression, Ki67 index, TP53 mutation status, presence of immune cells in the tumor microenvironment, and gene-mutation/expression profiling. Baseline tissue samples collected during screening will be shipped to a central laboratory for biomarker testing after local regulatory approval. This may occur after the start of study treatment if necessary.

For fresh biopsy specimens, acceptable samples include core needle biopsies for deep tumor tissue or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. Tumor tissue should be of good quality based on total and viable tumor content. Bone metastasis biopsy or cytological (fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage) samples are not acceptable. Enrollment of a patient who cannot provide sufficient tumor tissue or biopsy may be permitted on a case-by-case basis after discussion with the medical monitor and in consultation with the sponsor.

To explore resistance mechanisms, optional biopsies will be taken at accessible tumor sites from the patients who have confirmed disease progression during the study. Written patient consent is required for fresh tumor biopsies.

Blood samples will be collected at screening, time of first response, and time of disease progression. Blood-based biomarker analysis such as immune profiling, DNA and/or circulating tumor DNA sequencing, gene-expression profile, circulating free DNA assessment and cytokines profiling, plasma protein, etc, will be performed to explore their association with response, resistance, and prognosis. At the sites in mainland China, blood samples will be collected for immune profiling, DNA and/or circulating tumor DNA sequencing, gene-expression profiling, circulating free DNA assessment, and cytokine profiling.

For patients in Part A who have CLL/SLL, optional peripheral blood samples will be collected at the local laboratory at screening to assess risk factors, including status of TP53 mutation, IGHV mutation, 11q deletion, 13q deletion, and 17p deletion.

Part D and Part E

Tumor tissue must be sent to the central laboratory for analysis of potential predictors of response, including assessment of PI3Kδ and PD-L1 expression, TP53 mutation status, presence of immune cells in the tumor microenvironment genetic profiling, etc. A fresh tumor biopsy collected at screening is strongly recommended. If a fresh tumor biopsy is not available, an archival tissue sample (either an FFPE block with tumor tissue [preferred] or 10 to 15 unstained slides) is required. It is recommended that the archival tissue sample is collected within 2 years before screening. An optional biopsy after approximately 3 to 5 weeks of treatment is also strongly recommended for biomarker analysis to explore the relationships between biomarkers and preliminary anticancer activity of BGB-10188 in combination with tislelizumab. If feasible, any follow-up biopsy should ideally be taken from the same tumor lesion as the baseline biopsy to minimize the variance of tumor microenvironments due to the nature of different tissues (Oliver et al 2018; Kirkwood et al 2018). At the sites in mainland China, tissue will be obtained to assess PI3Kδ expression, PD-L1 expression, TP53 mutation status, presence of immune cells in the tumor microenvironment, and gene-mutation/expression profiling. Baseline tissue samples collected during the screening will be shipped to a central laboratory for biomarker testing after local regulatory approval. This may occur after the start of study treatment if necessary.

For fresh biopsy specimens, acceptable samples include core needle biopsies for deep tumor tissue or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. Tumor tissue should be of good quality based on total and viable tumor content. Bone metastasis biopsy or cytological (fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage) samples are not acceptable. Enrollment of a patient who cannot provide sufficient tumor tissue or biopsy may be permitted on a case-by-case basis after discussion with the medical monitor and in consultation with the sponsor.

To explore the resistance mechanism, optional biopsies will also be taken at accessible tumor sites from the patients who have confirmed disease progression during the study. If feasible, any follow-up biopsy should ideally be taken from the same tumor lesion as the baseline biopsy. Written patient consent is required for fresh tumor biopsies.

Blood samples will be collected at screening, C2D1, time of first response, and time of disease progression. Blood-based biomarker analysis such as DNA and/or circulating tumor DNA sequencing, gene-expression profile, circulating free DNA assessment, immune cell and cytokine profiling, plasma protein, etc, will be performed to explore their association with response, resistance, and prognosis. At the sites in mainland China, blood samples will be collected for immune profiling, DNA and/or circulating tumor DNA sequencing, gene expression profiling, circulating free DNA assessment, and cytokine profiling.

7.10. Unscheduled Visits

Unscheduled visits may be performed at any time at the patient's or the investigator's request and may include vital signs/targeted physical examination; ECOG Performance Status; AE review; concomitant medication and procedure reviews; radiographic assessments; physical

examination of liver, spleen, and lymph nodes; disease-related constitutional symptoms; and hematology and chemistry laboratory assessments. The date and reason for the unscheduled visit must be recorded in the source documentation.

If an unscheduled visit is necessary to assess toxicity or for suspected disease progression, then diagnostic tests may be performed based on the investigator assessment as appropriate, and the results of these tests should be entered on the unscheduled visit eCRF.

7.11. End-of-Treatment Visit

The End-of-Treatment (EOT) Visit is conducted within 7 days after the investigator determines that the patient must permanently discontinue BGB-10188, zanubrutinib, or tislelizumab. If routine laboratory tests (eg, hematology, clinical chemistry, coagulation, and urinalysis) were completed ≤ 7 days before the EOT Visit, these tests do not need to be repeated. A tumor assessment is not required at the EOT Visit if < 6 weeks have passed since the last assessment. If the EOT Visit did not occur until 30 days (± 7 days) or later after the last dose of BGB-10188, zanubrutinib, or tislelizumab, the EOT Visit may also be used as the Safety Follow-up Visit.

See Appendix 1 through Appendix 4 for assessments to be performed at the EOT Visit.

7.12. Follow-up Periods

7.12.1. Safety Follow-up Period

Patients who permanently discontinue study drug will be asked to return to the clinic for the Safety Follow-up Visit, which is required to be conducted 30 days (± 7 days) after the last dose of study drug (whichever is the latest) unless otherwise specified or before the initiation of subsequent anticancer therapy, whichever occurs first. The Safety Follow-up Visit may coincide with the EOT Visit (see Section 7.11) but cannot occur before the EOT Visit. For Parts A, B, and C, a laboratory assessment is required only if the patient had an ongoing laboratory abnormality at the previous visit that the investigator considered to be related to study drug. If the patient is unable to return to the clinic and no laboratory assessment is necessary, the investigator or his/her designee will contact the patient or guardian to collect information about AEs, including AEs that may have occurred or were ongoing after the patient discontinued study treatment.

For Part D and Part E, in addition, telephone contact with patients should be conducted to assess imAEs and concomitant medications (if appropriate, ie, associated with an imAE or is a subsequent anticancer therapy) at 60 and 90 days (± 14 days) after the last dose of study drug or before the initiation of a subsequent anticancer therapy, whichever occurs earlier. If a patient reports a suspected imAE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated.

All AEs, including SAEs, will be collected as described in Section 8.6.

See Appendix 1 through Appendix 4 for assessments to be performed at the EOT/Safety Follow-up Visit.

7.12.2. Survival Follow-up

After discontinuation of study treatment, patients in Part E will be followed for survival and further anticancer therapy information via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (± 14 days) after the EOT or Safety Follow-up Visit or as directed by the sponsor until death, loss to follow-up, withdrawal of consent, or study completion by the sponsor.

7.12.3. Lost to Follow-up

If attempts to contact the patient by telephone are unsuccessful, the following additional attempts should be made to obtain protocol-required follow-up information. The patient should be contacted by mail in a manner that provides proof of receipt by the patient. If unsuccessful, other contacts should be explored, such as referring physicians or relatives. Attempts to contact should be documented in the patient's source documents. If a patient cannot be contacted despite all attempts, the patient will be considered lost to follow-up, and death information should be obtained through a public record search if local agencies permit.

7.13. Discontinuation From Study Treatment or From the Study

7.13.1. Patient Discontinuation From Study Treatment

Patients have the right to discontinue study treatment at any time for any reason. In addition, the investigator has the right to discontinue a patient from study treatment at any time. Patients who will discontinue study treatment for reasons other than disease progression should be followed up for assessments of antitumor activity (Section 7.6), safety (Section 7.5), and survival (Section 7.12, if applicable), if possible.

The primary reason for discontinuation from study treatment should be documented on the appropriate eCRF. Patients may discontinue study treatment for reasons that include but are not limited to the following:

- Disease progression
- Adverse event
- Patient decision
- Pregnancy
- Any medical condition that the investigator or sponsor determines may jeopardize the patient's safety if he or she were to continue the study treatment
- Use of any concurrent anticancer therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents) for the treatment of cancer
- Patient noncompliance

7.13.2. Patient Discontinuation From the Study (End of Study for an Individual Patient)

Patients may discontinue from the study for reasons that include, but are not limited to, the following:

- Patient withdrawal of consent
- Death
- Loss to follow-up
- Patient completion of all study assessments
- Noncompliance

7.14. End of Study

The end of the study is defined as the timepoint when the final data point is collected from the last patient in the study. For each part of the study, the end of the part is when the last patient has been enrolled for 12 months in this part, or when the last patient dies, withdraws consent, completes all study assessments, or is lost to follow-up, whichever occurs earliest.

The sponsor has the right to terminate this study at any time. Reasons for terminating the study early include the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients.
- There is a lack of efficacy observed in the enrolled patients, and further enrollment is unlikely to bring benefits to patients with disease under study.
- Overall patient enrollment is unsatisfactory.
- A rollover study becomes available.

The sponsor will notify each investigator if a decision is made to terminate the study. Should this be necessary, prematurely discontinued patients must be seen for an EOT/Safety Follow-up Visit as described in Section 7.11 and Section 7.12.1.

The investigators may be informed of additional procedures to be followed to ensure that adequate consideration is given to the protection of the patients' interests. The investigator will be responsible for informing IRBs/IECs of the early termination of the study.

The sponsor has the right to close a site at any time. The decision will be communicated to the site in advance. Reasons for closing a site include but are not limited to the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Noncompliance with GCP or applicable laws and regulations
- Completion of study activity (ie, all patients have completed the study and all obligations have been fulfilled)

At the end of the study as determined by the sponsor, any patient who is still on treatment and, in the opinion of the investigator, continues to benefit from study drug treatment will continue treatment in a company-sponsored long-term extension study or a post-trial continued access

program or be kept in the study for continuous access of study drugs, whichever is available in the country of the patient's residence.

For the patient who is kept in the study for continuous access of study drugs after the end of the part/study, no data collection (except for SAEs or adverse events of special interest [AESI] through paper forms) will be conducted by the sponsor. For Parts A and B, the treatment access would be discontinued for reasons listed in Section 7.13.1 or when the continuous access was provided for approximately 1 year after the end of the corresponding part. For Part E, the treatment access would be discontinued for reasons listed in Section 7.13.1 or when the total treatment duration reaches 2 years. During the continuous study drug treatment, patient visits should be dependent on investigator's discretion.

8. SAFETY MONITORING AND REPORTING

The investigator is responsible for the monitoring and documentation of events that meet the criteria and definition of an AE or SAE as provided in this protocol.

8.1. Risks Associated With Study Drug

8.1.1. Risks Associated With BGB-10188

As of the data cutoff date of 05 February 2024, important potential risks for BGB-10188 treatment include hepatobiliary toxicity, diarrhea and colitis, rash, pneumonitis, and hypersensitivity.

Hepatobiliary toxicity was observed in 7 patients (20.6%) receiving BGB-10188 monotherapy (Part A). Four patients (11.8%) experienced Alanine aminotransferase increased, and 3 patients (8.8%) experienced Aspartate aminotransferase increased. Alanine aminotransferase increased and Hepatic function abnormal of Grade 3 were reported in 1 patient (2.9%) each.

For patients receiving BGB-10188 in combination with zanubrutinib (Part B), a total of 2 patients (50%) experienced Grade 3 Hypertransaminasaemia (1 patient), Grade 3 Alanine aminotransferase increased (1 patient), and Grade 3 Aspartate aminotransferase increased (1 patient).

For patients receiving BGB-10188 in combination with tislelizumab (Part D), 15 patients (34.1%) experienced Alanine aminotransferase increased, and 14 patients (31.8%) experienced Aspartate aminotransferase increased. Four patients (9.1%) experienced Grade 3 Aspartate aminotransferase increased, and 2 patients (4.5%) experienced Grade 3 Blood bilirubin increased. Grade 3 Abnormal hepatic function and Grade 4 Gamma-glutamyltransferase increased were reported in 1 patient each (2.3%).

For patients receiving BGB-10188 in combination with tislelizumab (Part E), 1 patient (16.7%) experienced Grade 3 Alanine aminotransferase increased and Grade 2 Aspartate aminotransferase increased.

Diarrhea and Colitis have been observed in 38.2% of patients receiving BGB-10188 monotherapy (Part A), and 25% of patients receiving BGB-10188 in combination with tislelizumab (Part D and Part E). Most events were mild, and no Grade 3 or higher Diarrhea and Colitis were reported for patients receiving BGB-10188 monotherapy. For Part D, 1 patient each (3 patients total, 6.9%) experienced Grade 3 Colitis (1 patient), Enterocolitis (1 patient), and Immune-mediated enterocolitis (1 patient). For Part E, 1 patient (16.7%) experienced Grade 3 Diarrhea.

Rash has been observed in 32.4% of patients treated with BGB-10188 in monotherapy and 28% in combination with tislelizumab; these events were generally mild to moderate in severity. One (2.9%) serious Grade 3 treatment-emergent adverse event of drug eruption was reported in the monotherapy cohort (Part A). Grade 3 Rash was also reported in 2 patients (4.5%) in Part D (combination with tislelizumab). No Grade 4 or higher events have been reported.

Pneumonitis has occurred in 8.8% of patients treated with BGB-10188 in monotherapy and 6.8% in combination with tislelizumab, including 1 serious adverse event of Grade 2

Immune-mediated lung disease in 1 patient treated with BGB-10188 in combination with tislelizumab. No Grade 3 or higher events have been reported.

As defined by the narrow scope Standardized MedDRA Query "anaphylactic reaction", no events were reported in Study BGB-A317-3111-10188-101. Of note, drug hypersensitivity (Grade 1 and 2) was reported in 2 patients (5.9%) and Grade 1 Angioedema was reported in 1 patient (2.9%) receiving BGB-10188 monotherapy (Part A). There were no drug hypersensitivity events described in combination therapy cohorts. No Grade 3 or higher events were reported.

Other potential risks for BGB-10188 treatment include phototoxicity, reproductive and development toxicity, and drug interaction.

8.1.1.1. Safety Data From Study BGB-10188-101

As of 05 February 2024, safety data are available from 88 patients exposed to BGB-10188 administered either as monotherapy or in combination with zanubrutinib or tislelizumab. The overall safety data have remained consistent with the expected safety profile. In total, 31 patients reported treatment-emergent SAEs; of these, 9 (26.5%) were reported from the BGB-10188 monotherapy cohort, 1 from the cohort receiving BGB-10188 in combination with zanubrutinib, and 21 (47.7%) from the cohort receiving BGB-10188 in combination with tislelizumab. Treatment-related SAEs were reported in 5 patients (14.7%) in BGB-10188 monotherapy and in 7 patients (15.9%) in BGB-10188 in combination with tislelizumab (200 mg).

The only treatment-emergent SAE by PT occurring in more than 1 patient receiving BGB-10188 monotherapy was Febrile neutropenia (2 patients, 5.9%).

The only treatment-emergent SAE by PT to occur in patients receiving BGB-10188 in combination with zanubrutinib was Grade 4 Acute myeloid leukaemia, which led to hospital prolongation. This serious adverse event was assessed as not related to study drugs by the investigator.

The most commonly (≥ 5%) occurring treatment-emergent SAEs by PT in patients receiving BGB-10188 in combination with tislelizumab were Alanine aminotransferase increased and Aspartate aminotransferase increased (4 patients each, 9.1%), followed by Pyrexia in 3 patients (6.8%).

As of the data cutoff date, a total of 5 patients within the 360 mg (2 patients) and 540 mg (3 patients) BGB-10188 monotherapy cohorts experienced a total of 6 adverse events that led to treatment discontinuation. Half of adverse events by SOC were Gastrointestinal disorders, but they were all single occurrences by PT (Flatulence, Eructation, Rash, Stomatitis, Face oedema, and Pneumonia). All these events were non-serious except Pneumonia. Four patients had BGB-10188-related adverse events that led to treatment discontinuation (Flatulence, Eructation, Rash, Stomatitis, and Pneumonia), and only 1 of them experienced a ≥ Grade 3 adverse event (Grade 3 Pneumonia). This patient recovered after discontinuing treatment and receiving concomitant medication.

As the data cutoff date, no patient receiving BGB-10188 in combination with zanubrutinib experienced adverse events that lead to treatment discontinuation.

A total of 8 patients receiving BGB-10188 in combination with tislelizumab (18.2%) experienced adverse events that led to discontinuation of study drug. Among them, 4 patients experienced adverse events that were considered as related to BGB-10188. For 2 patients receiving BGB-10188 160 mg in combination with tislelizumab 200 mg, 1 experienced Grade 3 Immune-mediated enterocolitis, and another experienced Grade 5 Pneumonia and Grade 5 Haemorrhage intracranial. For 2 patients receiving BGB-10188 320mg in combination with tislelizumab 200mg, 1 experienced Grade 3 decreased appetite, and another experienced Grade 3 Alanine aminotransferase increased and Grade 3 Aspartate aminotransferase increased.

Two patients with a DLT event were reported in the BGB-10188 monotherapy cohort, and 3 patients with a DLT event were reported in patients receiving BGB-10188 in combination with tislelizumab.

Two patients experienced TEAEs leading to death, of which 1 patient from BGB-10188 monotherapy cohort died due to the disease under study, and another patient from BGB-10188 160 mg in combination with tislelizumab 200 mg cohort due to Pneumonia and Haemorrhage intracranial and was considered as related to BGB-10188. Refer to the BGB-10188 Investigator Brochure for more details on the safety of BGB-10188.

Clinical experience with existing drugs in this therapeutic class (PI3K) suggests that patients may experience fatal and/or serious hepatotoxicity; diarrhea or colitis; pneumonitis; infection including pneumonia, CMV, and PJP; intestinal perforation; and severe cutaneous reactions.

The most common adverse reactions (incidence ≥ 20%) for approved agents from the same class of drugs are presented below.

- In patients treated with copanlisib: hyperglycemia (high blood sugar), diarrhoea, decreased general strength and decreased energy, hypertension (high blood pressure), leukopenia (low numbers of leukocytes, a type of WBC), neutropenia, nausea, lower respiratory tract infections, and thrombocytopenia (low numbers of blood platelets). Copanlisib can cause serious side effects, including infections, hyperglycemia, hypertension, pneumonitis, neutropenia, and skin rashes.
- In patients treated with duvelisib: diarrhoea or colitis, neutropenia, rash, fatigue, fever, cough, nausea, upper respiratory infection, pneumonia, musculoskeletal pain, and anaemia (low amounts of blood haemoglobin, which is associated with low numbers of red blood cells). Duvelisib has a US boxed warning due to the risk of these fatal and serious toxicities: infections, diarrhoea or colitis, skin reactions and pneumonitis.
- In patients treated with idelalisib: diarrhea, pneumonia, pyrexia, fatigue, rash, cough, and nausea. Common laboratory abnormalities were neutropenia, ALT elevations, and AST elevations. Idelalisib has a US boxed warning due to the risk of these fatal and serious toxicities: hepatotoxicity, severe diarrhea or colitis, pneumonitis, infections, and intestinal perforation.
- In patients treated with linperlisib: WBC count decreased, neutropenia, platelet count decreased, and anaemia.

Patients enrolled in this study must be closely monitored for the abovementioned or other AEs, and delay or interruption of BGB-10188 should be considered according to Section 5.5.1 and Section 5.6.

8.1.2. Risks Associated With Zanubrutinib

Zanubrutinib has received approvals for the indications of MCL, WM, MZL, CLL/SLL, and FL in over 65 countries/regions worldwide (including all EU states). Available data indicated that zanubrutinib was generally well tolerated at exposure levels resulting in complete and sustained BTK inhibition in patients with B-cell malignancies. Please refer to the zanubrutinib IB and zanubrutinib prescribing information for a summary of safety data and guidance for the investigator.

8.1.3. Risks Associated With Tislelizumab

Tislelizumab has been approved in China, Macao China, Europe, US, and South Korea. Tislelizumab is still in clinical development for other indications worldwide. Any recommendations are based on results from nonclinical and clinical studies with tislelizumab and published data on other molecules within the same biologic class. Refer to the tislelizumab IB for more details.

The PD-1/PD-L1 pathway is involved in peripheral immune tolerance; therefore, such therapy may increase the risk of imAEs, specifically the induction or enhancement of autoimmune conditions. Potential risks observed with anti-PD-1 therapy are presented in Section 8.7.1.

Although most imAEs observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Suggested evaluation and management guidelines for suspected imAEs are provided in Appendix 9.

8.2. General Plan to Manage Safety Concerns

8.2.1. Eligibility Criteria

Eligibility criteria were selected to guard the safety of patients in this study. Results from the nonclinical toxicology studies and clinical data with zanubrutinib and tislelizumab, as well as the nonclinical/clinical data from other drug classes, were considered. Specifically, patients at risk for study-emergent active autoimmune diseases, or with a history of autoimmune diseases that may relapse, patients who have undergone allogenic stem cell or organ transplantation and patients who have received a live viral vaccine within 28 days before the first dose of study drug are excluded from the study. See Section 4.2 for the full list of exclusion criteria.

8.2.2. Safety Monitoring Plan

Safety will be evaluated in this study through the monitoring of all AEs, defined and graded according to NCI-CTCAE v5.0. Patients will be assessed for safety (including laboratory values) according to the Schedule of Assessments in Appendix 1 through Appendix 4. Clinical laboratory results must be reviewed prior to the start of each cycle.

In this study, all enrolled patients will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of AEs, physical examinations, laboratory measurements (hematology, chemistry, etc) and other assessments. In addition, patients will be closely monitored for the development of any signs or symptoms of autoimmune conditions and infection.

Serum samples will be drawn for determination of ADAs to tislelizumab in patients in Part D and Part E. Administration of tislelizumab will be performed in a setting where emergency medical equipment and staff who are trained to respond to medical emergencies are available (see Section 5.2.3).

All AEs will be recorded during the study (AEs from the time of the first dose and SAEs from the time of signing of informed consent) and for up to 30 days after the last dose of study drug(s) or until the initiation of another anticancer therapy, whichever occurs first. At the end of treatment, ongoing AEs considered related to study treatment will be followed until the event has resolved to baseline or ≤ Grade 1, the event is assessed by the investigator as stable, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the AE.

Immune-mediated AEs will be recorded up to 90 days after the last dose of study drug or initiation of a subsequent anticancer therapy, whichever occurs earlier.

All drug-related SAEs will be recorded by the investigator until patient death, withdrawal of consent, or loss to follow-up, whichever occurs first.

Investigators are instructed to report all AEs (including pregnancy-related AEs).

The potential safety issues anticipated in this study, as well as measures intended to avoid or minimize such toxicities, are outlined in the following sections.

8.3. Adverse Events

8.3.1. Definitions and Reporting

An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study drug, whether considered related to study drug or not.

Examples of AEs include:

- Worsening of a chronic or intermittent pre-existing condition, including an increase in severity, frequency, or duration, and/or has an association with a significantly worse outcome
- New conditions detected or diagnosed after study drug 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 study drug or a concurrent medication (overdose per se should not be reported as an AE or SAE)

When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory results and diagnostics reports) relative to the AE or SAE. The investigator will then record all relevant information regarding an AE or SAE in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by the sponsor. In this instance, all patient identifiers will be blinded on the copies of the medical records prior to submission to the sponsor.

8.3.2. Assessment of Severity

The investigator will assess the severity of each AE and SAE reported during the study. AEs and SAEs should be assessed and graded based upon the NCI-CTCAE v5.0.

Toxicities that are not specified in the NCI-CTCAE v5.0 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 8.6.2.

8.3.3. Assessment of Causality

The investigator is obligated to assess the relationship between the study drug and the occurrence of each AE or SAE, using best clinical judgment. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the AE or SAE to the study drug should be considered and investigated. The investigator should consult the IB for BGB-10188, zanubrutinib, or tislelizumab 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 make an assessment of causality for every SAE prior to transmission of the SAE report to the sponsor, since the causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator may change his/her opinion of causality considering follow-up information, amending the SAE report accordingly.

Two-Point Causality Assessment

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 “a reasonable possibility” that the AE may have been caused by the study drug (ie, there are facts, evidence, or arguments to suggest possible causation). 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 criteria are met, otherwise the event should be assessed as not related:

- 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 patient’s clinical condition or other concomitant AEs)

8.3.4. Following Adverse Events

After the initial AE or SAE report, the investigator is required to proactively follow each patient and provide further information to the sponsor on the patient’s condition.

All AEs and SAEs documented at a previous visit/contact and designated as ongoing will be reviewed at subsequent visits/contacts.

All AEs and SAEs will be followed until resolution, the condition stabilizes or is considered chronic, the AE or SAE is otherwise explained, the patient is lost to follow-up, or the patient withdraws consent. 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, radiographic imaging, 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 patient 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 should be reported to the sponsor according to the SAE instructions provided by the sponsor within the timeframes outlined in Section 8.6.2.

8.3.5. Laboratory Test Abnormalities

Abnormal laboratory findings (eg, clinical chemistry, CBC, coagulation, or urinalysis) or other abnormal assessments (eg, ECGs, X-rays, or vital signs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs. 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 clinical significance is left to the judgment of the investigator. In general, these are the laboratory test abnormalities or other abnormal assessments that:

- are associated with clinical signs or symptoms, or
- require active medical intervention, or
- lead to dose interruption or discontinuation, or
- require close observation, more frequent follow-up assessments, or
- further diagnostic investigation.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (eg, ALP and bilirubin 5 x ULN associated with cholestasis), only the diagnosis (ie, cholestasis) should be recorded on the Adverse Event eCRF.

If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

8.4. 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 AE in which the patient was at risk of death at the time of the AE. It does not refer to an AE 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 patient was admitted (usually involving at least an overnight stay) to the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.

- 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 with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect
- Is considered a significant medical AE by the investigator based on medical judgment (eg, may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The following are NOT considered SAEs:

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline
- Hospitalization for social/convenience considerations
- Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience

8.5. Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is a serious adverse reaction that is both unexpected (ie, not present in the product's Reference Safety Information) and meets the definition of a serious adverse drug reaction, the specificity or severity of which is not consistent with those noted in the IB.

8.6. Timing, Frequency, and Method of Capturing Adverse Events and Serious Adverse Events

8.6.1. 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 either 30 days after the last dose of BGB-10188, zanubrutinib, or tislelizumab or until initiation of new anticancer therapy, whichever occurs first. Immune-mediated AEs (serious or nonserious) should be reported until 90 days after the last dose of study drug or initiation of a subsequent anticancer therapy, whichever occurs earlier. SAEs considered related to the study drug(s) that are brought to the attention of the investigator should be reported regardless of time since the last dose of treatment.

AEs and SAEs should be recorded according to the details in Table 12. For the follow-up period for AEs, see Section 8.3.4. For the definition of TEAEs, see Section 9.5.3.

Table 12: Guidance for Duration of Recording New or Worsening Adverse Events in All Treatment Arms

Event Type	Record New or Worsening Events That Occur During This Period	
	Begin	**End**
SAEs (not treatment-related)	Signing of informed consent	Up to 30 days after last dose, initiation of new anticancer therapy, death, withdrawal of consent, or loss to follow-up, whichever occurs first
Treatment-related SAEs	Signing of informed consent	Patient death, withdrawal of consent, or loss to follow-up, whichever occurs first
AEs due to PD	Do not record (see Section 8.6.5)	
Nonserious AEs	First dose of study drug	Up to 30 days after last dose, initiation of new anticancer therapy, death, withdrawal of consent, or loss to follow-up, whichever occurs first
Immune-mediated AEs (serious or nonserious)	First dose of study drug	Up to 90 days after last dose (or initiation of a subsequent anticancer therapy, whichever occurs earlier), death, withdrawal of consent, or loss to follow-up, whichever occurs first

Abbreviations: AE, adverse event; PD, progressive disease; SAE, serious adverse event.

8.6.2. Reporting Serious Adverse Events

8.6.2.1. Prompt Reporting of Serious Adverse Events and Adverse Events of Special Interest

As soon as the investigator determines that an AE meets the protocol definition of an SAE or adverse event of special interest of BGB-10188 (see Section 8.7.2), the event must be reported promptly (within 24 hours of site awareness) to the sponsor or designee as described in Table 13.

Table 13: Timeframes and Documentation Methods for Reporting Serious Adverse Events and Adverse Events of Special Interest to the Sponsor or Designee

	Timeframe for Making Initial Report	**Documentation Method**	**Timeframe for Making Follow-up Report**	**Documentation Method**	**Reporting Method**
All SAEs; AESI of BGB-10188 (see Section 8.7.2)	Within 24 hours of first knowledge of the SAE	SAE Report	Within 24 hours of site awareness	SAE Report	Email or fax SAE form

Abbreviations: AE, adverse event; AESI, adverse event of special interest; SAE, serious adverse event.

8.6.2.2. Completion and Transmission of the Serious Adverse Event Report and Adverse Events of Special Interest

Once an investigator becomes aware that an SAE or AESI (see Section 8.7.2) has occurred in a patient, he/she is to report the information to the sponsor within 24 hours as outlined above in Section 8.6.2.1. The SAE or AESI Report will always be completed as thoroughly as possible with all available details of the event and forwarded to the sponsor or designee within the designated timeframes.

If the investigator does not have all information regarding an SAE, he/she is not to wait to receive additional information before notifying the sponsor or designee of the SAE and completing the form. The form will be updated when additional information is received.

The investigator must always provide an assessment of causality for each SAE as described in Section 8.3.3.

The sponsor will provide contact information for SAE receipt.

8.6.2.3. 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 8.6.2.1. 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.

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 IRB/IEC.

All SUSARs (as defined in Section 8.5), will be submitted to all applicable regulatory authorities and investigators for BGB-10188, zanubrutinib, and tislelizumab studies.

When a study center receives an initial or follow-up safety report or other safety information (eg, revised IB) from the sponsor, the investigator or designated responsible person is required to promptly notify his/her IRB or IEC as per local regulations. The investigator should place copies of Safety Reports from the sponsor in the Investigator Site File.

8.6.3. 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?

8.6.4. Diagnosis Versus Signs and Symptoms

If a diagnosis is known at the time of reporting, this should be recorded in the eCRF (and SAE report, as applicable), rather than the individual signs and symptoms (eg, record only hepatitis rather than elevated transaminases, bilirubin, or jaundice). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time

of reporting, each individual AE should be recorded as an SAE or AE on the eCRF (and SAE report, if applicable). If a diagnosis is subsequently established, it should replace the individual signs and/or symptoms as the AE term on the eCRF (and SAE report, if applicable), unless the signs/symptoms are clinically significant.

8.6.5. Disease Progression

Progression of an underlying malignancy and related symptoms (including fatal outcomes) is not reported as an adverse event if it is clearly consistent with the expected pattern of progression of the underlying cancer. In most cases, the expected pattern of progression in Parts A and B will be based on Lugano criteria (Cheson 2014), while the expected pattern of progression in Parts D and E will be based on RECIST v1.1 (Eisenhauer et al 2009). In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through the use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event during the adverse event recording period on the Adverse Event eCRF, and immediately reported to the sponsor if assessed as a serious adverse event.

8.6.6. Death on Study

For deaths that occur during the study safety reporting period (refer to Section 8.6.1), regardless of relationship to study drug(s), the primary cause of death must be recorded as a fatal serious adverse event on the Adverse Event eCRF and be immediately reported to the sponsor.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown or if it is a sudden death, then the death could be recorded as an adverse event as “unknown cause of death” or “sudden death.”

8.6.7. Pregnancies

If a female patient or the partner of a male patient becomes pregnant while receiving study drugs, or within 90 days after the last dose of BGB-10188 and/or zanubrutinib (Parts A and B), or within 90 days after the last dose of BGB-10188 and/or 120 days after the last dose of tislelizumab (Parts D and E), a pregnancy report form is required to be completed and expeditiously submitted to the sponsor to facilitate outcome follow-up. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow-up will be no longer than 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered an AE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE.

An abortion, whether accidental, therapeutic, or spontaneous should be always reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a patient exposed to the study drug should be recorded and reported as an SAE.

8.6.8. Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Independent 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 Safety Information documents:

- Tislelizumab IB
- Zanubrutinib IB
- BGB-10188 IB

8.6.9. Assessing and Recording Immune-Mediated Adverse Events (Part D and Part E)

Since treatment with anti-PD-1 therapy can cause autoimmune disorders, AEs considered by the investigator to be immune-mediated (see Section 8.7.1.2) should be classified as imAEs and identified as such in the eCRF AE page until Day 90, after treatment discontinuation.

Investigators should consult the guidance on diagnostic evaluation and management of imAEs, which are commonly seen with immune CPIs, in Appendix 9.

An extensive list of potential imAEs appears in Section 8.7.1.2. All conditions similar to those listed should be evaluated to determine whether they are imAEs, based on a similar diagnostic process to those reactions that are presented in more detail in Appendix 9.

8.6.10. Assessing and Recording Infusion-Related Reactions (Part D and Part E)

The signs and symptoms of an IRR should be recorded as the adverse terms for those individual signs and symptoms. In assessing whether an AE is infusion related, note that the symptoms of IRRs may include, but are not limited to, 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, or cardiogenic shock.

8.7. Management of Adverse Event of Special Interest (AESI) (Part D and Part E)

8.7.1. AESI of Tislelizumab

IRRs, severe hypersensitivity reactions, and imAEs according to the NCI-CTCAE criteria are outlined below.

8.7.1.1. Infusion-Related Reactions and Hypersensitivity Reactions

Patients should be closely monitored during and after study drug administration for IRRs and hypersensitivity reactions. See Section 5.2.3 for the monitoring periods required. Immediate access to an Intensive Care Unit (ICU) or equivalent environment and appropriate medical

therapy (including epinephrine, corticosteroids, antihistamines, bronchodilators, and oxygen) must be available to treat IRRs.

See Table 14 for management of IRRs and hypersensitivity reactions as well as treatment modifications.

8.7.1.2. Immune-Mediated Adverse Events

In this study, imAEs are of special interest. Potential imAEs are listed in Table 15 below. All AEs similar to those listed in the table should be evaluated in patients receiving tislelizumab to determine whether the AE is immune mediated. The investigator should exclude alternative explanations (eg, combination drugs, infectious disease, metabolic causes, toxins, disease progression, or other neoplastic causes) with appropriate diagnostic tests that may include, but are not limited to, serologic, immunologic, and histologic (biopsy) data (see Appendix 9). If alternative causes have been ruled out and the AE required the use of systemic steroids, other immunosuppressants, or endocrine therapy, and it is consistent with an immune-mediated mechanism of action, the imAE indicator in the eCRF AE page should be checked.

Recommendations for managing imAEs are detailed in Appendix 9.

Table 14: Treatment Modifications for Symptoms of Infusion-Related Reactions Due to Study Drug(s)

NCI-CTCAE Grade	Treatment Modification for Tislelizumab
Grade 1 – mild 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 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h.	Stop infusion. Infusion may be resumed at 50% of previous rate once infusion-related reactions has resolved or decreased to 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.

Table 15: Examples of Immune-Mediated Adverse Events

Body System Affected	Events
Skin (mild-common)	Pruritus or maculopapular rash; vitiligo
Skin (moderate)	Follicular or urticarial dermatitis; erythematous/lichenoid rash; Sweet 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; 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
Musculoskeletal	Arthritis; arthralgia; myalgia; myasthenic syndrome/myasthenia gravis; myositis
Blood	Anemia; leukopenia; thrombocytopenia
Renal	Interstitial nephritis; glomerulonephritis; acute renal failure
Cardiac	Pericarditis; myocarditis; heart failure
Neurologic	Encephalitis; Guillain-Barré syndrome; meningitis; meningoradiculitis; meningoencephalitis; neuropathy

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

8.7.2. AESI of BGB-10188

Adverse events of special interest of BGB-10188 (whether nonserious or serious) are required to be reported by the investigator to the sponsor immediately (ie, no more than 24 hours after learning of the event) following the same requirements and procedure as described in Section 8.6.2.1 and Section 8.6.2.2. Adverse events of special interest of BGB-10188 for this study are as follows:

- Any treatment-emergent diarrhea:
  - ≥ Grade 2 diarrhea
  - ≥ Grade 1 diarrhea lasting for more than 7 days

9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

The statistical analyses will be performed by the sponsor or designee after the data collection is completed for the planned analysis and the database is locked and released. Statistical analyses that support model-based dose escalation will be performed recurrently before each SMC meeting that decides the dose level for next group of patients or enroll more eligible patients. Details of the statistical analyses will be included in a separate Statistical Analysis Plan (SAP).

Please see Section 2 for study objectives.

9.1. Bayesian Model-based Dose Escalation Design

Model-based dose escalation methods will be used for monotherapy in Part A and combination therapy with tislelizumab in Part D to adaptively recommend dose for new cohort and end of dose escalation phase and recommendation of MTD. The model recommendation is non-binding and the decision of next dose and/or eventually the identification of RDFE will be made by the SMC based on the totality of data, given the safety of trial patients is protected. Rule-based modified 3 + 3 design will be used for dose escalation for combination therapy with zanubrutinib in Part B. The algorithm is provided in Section 3.2.2.

9.1.1. Planned Dose/Combination Levels

In Part A, 5 proposed dose levels of BGB-10188 monotherapy will be tested in mature B-cell malignancies: 60 mg once daily, 120 mg once daily, 240 mg once daily, 360 mg once daily, and 540 mg once daily. Additional dose levels or schedule could be added if deemed appropriate.

In Part B, dose escalation of BGB-10188 in combination with zanubrutinib 160 mg twice daily will start at the latest cleared dose in Part A.

In Part C, dose expansion of BGB-10188 in combination with zanubrutinib 160 mg twice daily will start at the RDFE identified from Part B.

In Part D, when BGB-10188 monotherapy dose level 120 mg once daily has been cleared, start of dose escalation in combination with tislelizumab in advanced solid tumor will be triggered. In combination with tislelizumab 200 mg once every 3 weeks, 6 proposed dose levels of BGB-10188 are planned: 20 mg once daily, 40 mg once daily, 80 mg once daily, 160 mg once daily, 320 mg once daily, and 540 mg once daily. The dose levels and dosages of BGB-10188 may be adjusted according to the safety and exposure result in Part A and additional dose levels may be added if deemed appropriate.

In Part E, dose expansion of BGB-10188 in combination with tislelizumab 200 mg once every 3 weeks will start at the RDFE identified from Part D.

9.1.2. Cohort Size

A cohort in the dose escalation step is defined as a set of patients sequentially enrolled and administered at the dose level recommended for the cohort. The size of a cohort is approximately 3 patients.

9.1.3. Statistical Models

A Bayesian model-based dose escalation approach will be used for dose escalation for monotherapy BGB-10188 in Part A and combination therapy of BGB-10188 and tislelizumab in Part D. At the time of dose recommendation for new cohort, the model will estimate DLT rate of each dose based on data collected from all the cohorts of patients by the time, not only the limited data from patients only from the current cohort. Two types of statistical models will be used: A Bayesian logistic regression model (BLRM, Neuenschwander et al 2008) will be used to model dose relationship with the early-onset DLT events that occur within the 28-day observation period ("early-onset"); additionally, as a further step of protection against overdosing considering both early and late-onset DLT events until 8 weeks, a Bayesian proportional hazard (BPH) model similar to Tighiouart et al (2014) will be used to account for the overall toxicity level until 8 weeks. However, the BPH models do not require all the patients to complete the 8-week late-onset events observation period before next dose decision can be made. They will use all the available data collected up to each dose decision point to estimate the DLT rate of both early and late-onset events up to 8 weeks for each dose/combination. Those 2 models will be used jointly to help recommend next dose/combination.

9.1.3.1. Bayesian Logistic Regression Model

A BLRM (Neuenschwander et al 2008) will be used to model dose relationship with the early-onset DLT events, up to the end of 28-day observation period.

Part A BGB-10188 Monotherapy

For monotherapy in Part A, a two-parameter BLRM (Neuenschwander et al 2008) will be used for BGB-10188 dose escalation. All the current and previous cohorts' data will be used to continuously update the model. The model will estimate distribution of the toxicity (DLT rate) at each dose level, which will be classified into 3 categories: underdosing (DLT rate ≤ 0.167), target toxicity (DLT rate between 0.167 and 0.333), and overdosing (DLT rate ≥ 0.333), based on which the dose recommendation will be primarily made.

Part D Combination Therapy With Tislelizumab

For combination therapy in solid tumors in Part D, a similar two-parameter BLRM model will be used to model the dose relationship with the joint toxicity of BGB-10188 and tislelizumab 200 mg once every 3 weeks. The model parameters can be considered reflecting the toxicity induced by BGB-10188 in conjunction with a potential synergistic effect from the combination therapy. Therefore, different prior settings will be adopted based on the candidate dose levels considered for the combination therapy.

9.1.3.2. Bayesian Proportional Hazard Model

BPH models in the same spirit of Tighiouart et al (2014) will be used to further take into account the late-onset DLT events within the 8-week observation period as a gate keeping criterion for dose escalation and MTD recommendation.

Part A BGB-10188 Monotherapy

The BPH method models patients' DLT hazard over time based on the BGB-10188 doses they received from C1D1. In order to incorporate all DLT events in the model, including those that occurred within the first 28 days and the events that occurred after 28 days but within 8 weeks, a three-parameter BPH model will be used, which assumes different baseline hazards for the first 28 days and for the remaining period until 8 weeks.

For patients with a DLT observed within 8 weeks, actual time to the onset of the DLT will be used and considered an event. For patients without a DLT observed, time to the end of the observation period or 8-weeks whichever is earlier will be used and considered censored.

Part D Combination Therapy With Tislelizumab

The BPH model for BGB-10188 dose escalation combination with tislelizumab at 200 mg once every 3 weeks will be similar to the monotherapy dose escalation in Part A, except that different prior range of MTD will be adopted to consider potentially different toxicity profile induced by BGB-10188 in conjunction with a possible synergistic effect from the combination therapy with tislelizumab.

9.1.4. Next Dose Recommendation Rules

For both Part A and Part D, next dose recommendation from the models will be a dose/combination that

- has the highest posterior probability falling into the target toxicity interval (DLT rate between 0.167 and 0.333) based on BLRM, and
- has a posterior probability in the overdosing interval (DLT rate ≥ 0.333) not exceeding 0.25 threshold based on BLRM, and
- satisfies the overdosing protection criterion based on BPH model, ie, with a posterior probability in the overdosing interval (overall DLT rate ≥ 0.333) not exceeding a 0.5 threshold; in other words, the estimated posterior median overall DLT rate including the potential late-onset events of the recommended dose cannot exceed 0.333.

A dose can be recommended for next cohort only when the dose satisfies both BLRM and BPH models' criteria.

Dose escalation will be indicated if the dose satisfying the above criteria is higher than the current dose. In general, dose skipping for a dose escalation is not allowed. Dose de-escalation will be indicated if the dose satisfying the above criteria is a dose lower than the current dose.

The dose recommendation is non-binding by the 2 models and will be made along with other related available information. The SMC will make the recommendation on the dose level for the next cohort.

9.1.5. Escalation Phase Stopping and MTD Recommendation Rules

For both Part A and Part D, the models will recommend an end of dose escalation when one of the following criteria is met:

- The next dose recommended has been tested on ≥ two previous cohorts and the probability that the DLT rate for this dose falls into the target toxicity interval (between 16.7% and 33.3%) is greater than 50%, or
- The next dose recommended has been used in the 2 immediately previous cohorts, or
- The next dose recommended has been used in 3 previous cohorts, or
- No dose can be recommended, or
- The maximal allowable sample size is reached.

When the dose escalation is stopped due to any of above reasons, the MTD is the dose level with the highest probability that its DLT rate falls into the target toxicity interval while the probability that it falls into the overdosing interval is controlled as described in Section 9.1.4. The RDFE may be determined based on the totality of safety, PK, efficacy, and/or any other relevant data as well as the MTD recommended by the BLRM and BPH models.

9.2. Study Endpoints

Part A: BGB-10188 Monotherapy

Primary Endpoint

- The RDFE of BGB-10188 monotherapy in hematologic malignancies.
- The incidence and severity according to NCI-CTCAE v5.0 of TEAEs, SAEs, and AEs leading to discontinuation of BGB-10188

Secondary Endpoints

- ORR by disease type defined as the proportion of patients achieving
  - CR, complete response with incomplete marrow recovery, PR, or partial response with lymphocytosis for CLL as per the 2018 iwCLL guidelines (Hallek et al 2018) with modification for treatment-related lymphocytosis (Cheson et al 2012)
  - PR or better for MCL, MZL, FL, and SLL as per the Lugano Classification for NHL (Cheson et al 2014)
- PK characteristics of BGB-10188 including plasma concentrations of BGB-10188 as a function of time and PK parameters for single (first) dose and multiple doses

Exploratory Endpoints

- Correlation between BGB-10188 concentrations and corrected QT intervals
- Pharmacodynamic biomarkers (eg, phospho-AKT level in normal or malignant B cells) will be assessed after single (first) dose and multiple doses of BGB-10188
- Identification of mutations or signatures associated with resistance and other biomarkers (eg, proportion and absolute number of Treg cells in peripheral blood or in tumor tissue, mutation profile, PI3K expression level, etc) will be correlated with efficacy of BGB-10188 monotherapy in the evaluated disease types.

Part B: BGB-10188 + Zanubrutinib Dose Escalation

Primary Endpoint

- The RDFE of BGB-10188 in combination with zanubrutinib in hematologic malignancies.
- The incidence and severity according to NCI-CTCAE v5.0 of TEAEs, SAEs, and AEs leading to discontinuation of BGB-10188 in combination with zanubrutinib

Secondary Endpoints

- Secondary antitumor endpoints as determined by investigator per the Lugano Classification for NHL (Cheson et al 2014) are as follows:
  - ORR defined by disease type as the proportion of patients achieving partial response or better for MCL, FL, and DLBCL
  - DOR defined as the time from the first response documentation to the date that progression is documented after treatment initiation or death, whichever occurs first.
  - TTR defined as the time from treatment initiation to the first documentation of response.
- PK characteristics of BGB-10188 including plasma concentrations as a function of time and PK parameters for single (first) dose and multiple doses

Exploratory Endpoints

- Identification of mutations or signatures associated with resistance and biomarkers (eg, proportion and absolute number of Treg cells in peripheral blood or in tumor tissue, mutation profile, PI3K expression level, etc) will be correlated with efficacy of BGB-10188 in combination with zanubrutinib, in the evaluated disease types.
- Plasma concentrations and PK parameters of zanubrutinib
- Pharmacodynamic biomarkers (eg, phospho-AKT level in normal or malignant B cells) will be assessed after single (first) dose and multiple doses of BGB-10188.

Part C: BGB-10188 + Zanubrutinib Dose Expansion

Primary Endpoint

- ORR by disease type defined as the proportion of patients achieving partial response or better for FL, MCL, and DLBCL as per the Lugano Classification for NHL (Cheson et al 2014)

Secondary Endpoints

- Secondary antitumor endpoints as determined by investigator per the Lugano Classification for NHL (Cheson et al 2014) are as follows:
  - DOR
  - TTR
  - PFS defined as time from treatment initiation to documentation of progression or death due to any cause, whichever happens first
- The incidence and severity according to NCI-CTCAE v5.0 of TEAEs, SAEs, and AEs leading to discontinuation of BGB-10188 + zanubrutinib
- PK characteristics of BGB-10188 including plasma concentrations as a function of time and PK parameters for single (first) dose and multiple doses

Exploratory Endpoints

- OS defined as the time from treatment initiation until death.
- Identification of mutations or signatures associated with resistance and biomarkers (eg, proportion and absolute number of Treg cells in peripheral blood or in tumor tissue, mutation profile, PI3K expression level, etc) will be correlated with efficacy of BGB-10188 in combination with zanubrutinib, in the evaluated disease types.
- Plasma concentrations and PK parameters of zanubrutinib
- Pharmacodynamic biomarkers (eg, phospho-AKT level in normal or malignant B cells) will be assessed after single (first) dose and multiple doses of BGB-10188.

Part D: BGB-10188 + Tislelizumab Dose Escalation

Primary Endpoints

- The RDFE of BGB-10188 in combination with tislelizumab in advanced solid tumors
- The incidence and severity according to NCI-CTCAE v5.0 of TEAEs, SAEs, and AEs leading to discontinuation of BGB-10188 in combination with tislelizumab

Secondary Endpoints

- ORR, DOR, DCR, and TTR as assessed using RECIST v1.1
- PK characteristics of BGB-10188 in combination with tislelizumab including plasma concentrations of BGB-10188 as a function of time and PK parameters for single (first)

dose and multiple doses

Exploratory Endpoints

- Immunogenic responses to tislelizumab, evaluated through the detection of ADA
- Pharmacodynamic biomarkers (eg, phospho-AKT level in B cells or T cells, change of immune cell profiling) will be assessed after single (first) dose and multiple doses of BGB-10188 in combination with tislelizumab.
- Identification of mutations or signatures associated with resistance and other biomarkers (eg, proportion and absolute number of Treg cells in peripheral blood or in tumor tissue, mutation profile, PI3K and/or PD-L1 expression level, etc) will be correlated with the preliminary anticancer activity of BGB-10188 in combination with tislelizumab in patients with advanced solid tumors.

Part E: BGB-10188 + Tislelizumab Dose Expansion

Primary Endpoints

- ORR as assessed using RECIST v1.1 per investigator
- The incidence and severity according to NCI-CTCAE v5.0 of TEAEs, SAEs, and AEs leading to discontinuation of BGB-10188 in combination with tislelizumab

Secondary Endpoints

- DOR, PFS, DCR, clinical benefit rate, and TTR as assessed using RECIST v1.1
- Locally assessed CA-125 response rate per Gynecological Cancer Intergroup (Appendix 20)
- PK characteristics of BGB-10188 in combination with tislelizumab including plasma concentrations of BGB-10188 as a function of time and PK parameters for single (first) dose and multiple doses

Exploratory Endpoints

- Immunogenic responses to tislelizumab, evaluated through the detection of ADAs
- Pharmacodynamic biomarkers (eg, phospho-AKT level in B cells or T cells, change of immune cell profiling) will be assessed after single (first) dose and multiple doses of BGB-10188 in combination with tislelizumab
- Identification of mutations or signatures associated with resistance and other biomarkers (eg, proportion and absolute number of Treg cells in peripheral blood or in tumor tissue, mutation profile, PI3K and/or PD-L1 expression level, etc) will be correlated with the preliminary anticancer activity of BGB-10188 in combination with tislelizumab in patients with PROC

9.3. Statistical Analysis

Data will be listed and summarized according to the sponsor-agreed reporting standards, where applicable, by study part and further by indication and dose level if specified. All analyses will be conducted in appropriate analysis sets as specified below.

9.3.1. Analysis Sets

9.3.1.1. Part A, Part B, and Part C

- DLT-Evaluable set is defined as all patients who received ≥ 75% of the scheduled dose of each study treatment during the first 28-day treatment cycle. Additionally, patients who had a DLT event during the corresponding DLT observation window despite having received < 75% of the scheduled dose will also be considered evaluable.
- Safety Analysis Set is defined as all patients who received at least one medication of BGB-10188 and/or zanubrutinib (for combination therapy part). This will be the primary analysis set used for safety analyses.
- Efficacy Analysis Set is defined in the same way as the Safety Analysis Set and will be the primary analysis set used for efficacy analyses.
- PK Analysis Set is defined as all patients who had ≥ 1 postdose plasma concentration and no important protocol deviation affecting PK.

9.3.1.2. Part D

- DLT-Evaluable Set is defined as all patients who received ≥ 75% of the scheduled dose of BGB-10188, ≥ 75% of the scheduled dose of tislelizumab during the first 28-day treatment cycle. Additionally, patients who had a DLT event during the corresponding DLT observation window despite having received < 75% of scheduled dose of tislelizumab or < 75% of the scheduled dose of BGB-10188 will also be considered evaluable.
- Safety Analysis Set is defined as all patients who received at least one medication of BGB-10188 and/or tislelizumab. This will be the primary analysis set used for safety analyses.
- The Efficacy Analysis Set is defined in the same way as the Safety Analysis Set and will be the primary analysis set used for efficacy analyses.
- The PK Analysis Set is defined as all patients who had ≥ 1 postdose plasma concentration and no important protocol deviation affecting PK.

9.3.1.3. Part E

- The Safety Analysis Set is defined as all patients who received at least one medication of BGB-10188 and/or tislelizumab. Patients are analyzed according to the treatment they actually received. This will be the primary analysis set used for safety analyses.
- The Efficacy Analysis Set follows the modified intent-to-treat principle and includes all patients who are randomized/enrolled and treated. The patients will be analyzed

according to the treatment group to which they were randomized/enrolled to. The Efficacy Analysis Set will be the primary analysis set used for efficacy analyses.

- The Efficacy Evaluable Analysis Set includes all patients who received at least one dose of study drugs, have evaluable disease at baseline, and have at least one evaluable postbaseline tumor response assessment unless any clinical disease progression or death occurred before the first postbaseline tumor assessment. The Efficacy Evaluable Analysis Set will be the sensitivity analysis set for efficacy analyses.
- The PK Analysis Set is defined as all patients who had at least one postdose plasma concentration and no important protocol deviation affecting PK.

9.3.2. Randomization Method (Part E)

In Part E, patients will be randomized at a 2:1 ratio to receive either BGB-10188 160 mg once daily plus tislelizumab 200 mg once every 3 weeks or BGB-10188 320 mg once daily plus tislelizumab 200 mg once every 3 weeks. The randomization will be performed centrally using the IRT system on or immediately prior to Cycle 1 Day 1.

9.3.3. Patient Disposition

The number of patients enrolled, treated, and discontinued from study drug or study will be summarized. The primary reason for study drug discontinuation will be summarized according to the categories recorded in the eCRF. The end of study status (alive, death, withdrew consent, or lost to follow up) at the data cutoff date will be summarized using the data from the eCRF.

9.3.4. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized descriptively. Continuous variables include but not limited to age, weight, vital signs, time since initial disease diagnosis, etc; categorical variables include but not limited to sex, age group, disease stage, ECOG, prior line of therapy, etc.

9.3.5. Disease History

The number (percentage) of patients reporting a history of disease and characteristic will be summarized descriptively. Disease characteristics include but not limited to time since first diagnosis of disease to study entry, time from most recent relapse or refractory to study entry, disease subtype, etc.

9.3.6. Prior and Concomitant Medications

Prior and concomitant medications will be assigned a preferred name using the World Health Organization Drug Dictionary drug codes. Prior and concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical (ATC) class indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by preferred name and therapeutic class. Prior medications will be defined as medications that started before the day of first dose of study drug. Concomitant medications will be defined as medications that 1) started before the first dose of study drug and were continuing at the time of the first dose of

study drug, or 2) started on or after the date of the first dose of study drug up to 30 days after the patient's last dose.

9.3.7. Medical History

Medical history will be mapped to a SOC and a PT using the MedDRA of the version currently in effect at BeiGene at the time of database lock. The number (percentage) of patients reporting a history of any medical condition, as recorded on the CRF, will be summarized by SOC and PT.

9.4. Efficacy Analyses

Efficacy assessments will use the applicable criteria to assess related efficacy endpoints (Appendix 13, Appendix 14, and Appendix 17). Analyses will be conducted by study part (where applicable) and indication based on the Efficacy Analysis Set.

9.4.1. Part A, Part B, and Part C

Overall Response Rate (ORR)

ORR will be estimated as crude proportion of patients achieving PR with lymphocytosis or better for CLL patients by investigator; and PR or better for MCL, MZL, FL, DLBCL, and SLL patients by investigator. Two-sided Clopper-Pearson 95% CI of ORR will be constructed to assess the precision of the point estimate of ORR.

Best overall response is defined as the best response recorded from the start of treatment to the end of the best response determination period. The proportion for each response category (CR, PR, stable disease, and disease progression) will be presented. Patients with no postbaseline response assessment (due to any reason) will be considered as non-responders for best overall response.

Progression-free Survival (PFS)

PFS is defined as time from treatment initiation to documentation of progression or death due to any cause, whichever happens first assessed by investigator. The median and other quartiles of PFS will be estimated by the Kaplan-Meier method. The 2-sided 95% CIs of median and other quartiles will be constructed using the Brookmeyer and Crowley method (Brookmeyer and Crowley 1982). Event-free rates at selected timepoints for PFS will be estimated using the Kaplan-Meier method with their 2 sided 95% CIs based on the Greenwood formula (Kalbfleisch and Prentice 1980).

More details including the censoring rules will be provided in the SAP.

Duration of Response (DOR)

DOR is defined as the time from the first determination of an objective response to the date that progression is documented after treatment initiation assessed by investigator or death, whichever occurs first. DOR will be analyzed using the same methods as PFS, but only for patients who have achieved an overall response of at least PR. The distribution of DOR will be summarized by the Kaplan-Meier method.

Overall Survival (OS)

OS is defined as the time from treatment initiation until death. OS will be analyzed using the similar methods employed for the PFS analysis except for the censoring rules.

Time to Response (TTR)

TTR is defined as the time from treatment initiation to the first documentation of response assessed by investigator. TTR will be summarized only for responders by descriptive statistics.

Other Efficacy Analyses

Exploratory endpoints, including but not limited to correlation of clinical response to BGB-10188 or in combination with zanubrutinib and biomarker characteristics (eg, presence of Treg cells in peripheral blood or in tumor tissue, mutation profile, PI3K expression, etc), will be explored.

9.4.2. Part D

Overall Response Rate (ORR)

ORR is defined as the proportion of patients achieving PR or better assessed by the investigator using RECIST v1.1 and will be analyzed the same way as in Section 9.4.1.

Duration of Response (DOR)

DOR is defined as the time from the first determination of an objective response per RECIST v1.1 until the first documentation of progression assessed by investigator or death, whichever comes first, and will be analyzed the same way as in Section 9.4.1.

Disease Control Rate (DCR)

DCR is defined as the proportion of patients with best overall response, as defined in RECIST v1.1, of a CR, PR, and stable disease assessed by investigator. This will be summarized similarly as ORR. Two-sided Clopper-Pearson 95% CI of DCR will be constructed.

Time to Response (TTR)

TTR is defined as the time from treatment initiation to the first documentation of response assessed by investigator. TTR will be analyzed the same way as in Section 9.4.1.

Other Efficacy Analyses

Exploratory endpoints, including but not limited to correlation of clinical response to BGB-10188 in combination with tislelizumab and biomarker characteristics (eg, presence of Treg cells in peripheral blood or in tumor tissue, tumor mutation profile, tumor microenvironment, etc), will be explored.

9.4.3. Part E

Overall Response Rate (ORR)

ORR is defined as the proportion of patients achieving PR or better assessed by the investigator using RECIST v1.1 and will be analyzed the same way as in Section 9.4.1.

CA-125 Response Rate

CA-125 response rate is defined as the proportion of patients achieving a CA-125 response according to the Gynecological Cancer Intergroup criteria. A response has occurred if there is at least a 50% reduction in CA-125 levels from baseline. Patients can be evaluated according to CA-125 only if they have a pretreatment sample that is at least twice the upper limit of normal and within 2 weeks prior to starting treatment. Two-sided Clopper-Pearson 95% CI of CA-125 rate will be constructed to assess the precision of the point estimate.

Duration of Response (DOR)

DOR is defined as the time from the first determination of an objective response per RECIST v1.1 until the first documentation of progression assessed by the investigator or death, whichever comes first, and will be analyzed the same way as in Section 9.4.1.

Progression-free Survival (PFS)

PFS is defined as the time from treatment initiation to the date of the first documentation of disease progression assessed by the investigator using RECIST v1.1 or death, whichever occurs first. The median and other quartiles of PFS will be estimated by the Kaplan-Meier method. The 2-sided 95% CIs of median and other quartiles will be constructed using the Brookmeyer and Crowley method (Brookmeyer and Crowley 1982). Event-free rates at selected timepoints for PFS will be estimated using the Kaplan-Meier method with their 2 sided 95% CIs based on the Greenwood formula (Kalbfleisch and Prentice 1980).

More details including the censoring rules will be provided in the SAP.

Disease Control Rate (DCR)

DCR is defined as the proportion of patients with best overall response, as defined in RECIST v1.1, of a CR, PR, or stable disease assessed by the investigator. This will be summarized similarly as ORR. Two-sided Clopper-Pearson 95% CI of DCR will be constructed.

Clinical Benefit Rate

Clinical benefit rate is defined as the proportion of patients with best overall response, as defined in RECIST v1.1, of a CR, PR, or at least 24 weeks of stable disease assessed by the investigator. This will be summarized similarly as ORR. Two-sided Clopper-Pearson 95% CI of DCR will be constructed.

Time to Response (TTR)

TTR is defined as the time from treatment initiation to the first documentation of response assessed by the investigator. TTR will be analyzed the same way as in Section 9.4.1.

Other Efficacy Analyses

Exploratory endpoints, including, but not limited to, correlation of clinical response to BGB-10188 in combination with tislelizumab and biomarker characteristics (eg, presence of Treg cells in peripheral blood or in tumor tissue, tumor mutation profile, tumor microenvironment, etc), will be explored.

9.5. Safety Analyses

The safety analyses will be conducted by study part, indication, dose level, and overall, as appropriate based on the Safety Analysis Set.

9.5.1. Extent of Exposure

Extent of exposure to the study drugs will be summarized descriptively as the number of cycles received (number and percentage of patients), duration of exposure (days), cumulative total dose received per patient (mg), dose intensity (mg/day), and relative dose intensity.

The number (percentage) of patients requiring dose interruption and dose delay/reduction will be summarized. The frequency of the dose interruption/delay/reduction and the cycle in which the first dose interruption/delay/reduction occurred will be summarized descriptively.

9.5.2. Dose-Limiting Toxicities

DLT events will be summarized by dose level and study part in the dose escalation phase.

9.5.3. Adverse Events

The AE verbatim descriptions (investigator's description from the eCRF) will be coded using MedDRA. AEs will be coded to MedDRA lower level term, PT, and primary SOC.

A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug up to 30 days following study drug discontinuation (the last one for combination therapies) or initiation of a new anticancer therapy, whichever occurs first. Worsening of an event to Grade 5 TEAE beyond Day 30 after the last dose of study drugs is also considered a TEAE (if it is prior to the start of a new anticancer therapy). Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in patient data listings.

For Part D and Part E, imAEs will be identified from all AEs that had an onset date or worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to 90 days from the last dose of study drug or initiation of a subsequent anticancer therapy, whichever occurs earlier.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by SOC and PT. A patient will be counted only once by the highest severity grade per NCI-CTCAE v5.0 within an SOC and PT, even if the patient experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of patients with TEAEs will also be summarized by relationship to the study drug. Treatment-related AEs include those events considered by the investigator to be related to treatment or with missing assessment of the causal relationship.

SAEs, deaths, TEAE with ≥ Grade 3, imAE (for Part D and Part E), treatment-related TEAEs, and TEAEs that led to treatment discontinuation and/or dose modification, dose interruption, or dose delay will be summarized.

9.5.4. Laboratory Analyses

CBC, serum chemistry, coagulation, and urinalysis values will be evaluated for each laboratory parameter. Abnormal laboratory values will be flagged and identified as those outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be included in the clinical study report. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) for

laboratory parameters and their changes from baseline will be calculated. Laboratory values will be summarized by visit and by worst postbaseline visit.

Laboratory parameters that are graded in NCI-CTCAE v5.0 or iwCLL (2018) will be summarized by NCI-CTCAE grade or iwCLL grade accordingly. In the summary of laboratory parameters by grade, parameters with grading in both high and low directions (eg, calcium, glucose, magnesium, potassium, sodium) will be summarized separately.

9.5.5. Vital Signs Analyses

Descriptive statistics for vital sign parameters (eg, systolic and diastolic BP, heart rate, temperature) and changes from baseline will be presented by visit.

9.5.6. Ophthalmologic Examination (Part D)

Ophthalmologic examination results will be listed by patient.

9.6. Pharmacokinetic Analyses

For the PK evaluation of BGB-10188 and zanubrutinib, plasma concentration-time data of each patient will be tabulated and graphically presented on linear semi-logarithmic scales. PK parameters will be determined using a standard noncompartmental method. A listing of patients excluded from the analysis set and individual data points excluded from the analysis will be provided. The PK parameters will be summarized with descriptive statistics (N, arithmetic mean, standard deviation, minimum, median, maximum, geometric mean, and coefficient of variation (CV) % associated to the geometric mean).

PK parameters will include, but are not limited to, the following as allowed by data:

C_{max} (µg/mL)	Observed maximum plasma concentration during a sample interval
C_{τ} (µg/mL)	Observed trough concentration at steady state
T_{max} (hr)	Observed time to maximum plasma concentration during a sampling interval
$t_{½}$ (h)	Terminal elimination half-life, determined from the quotient 0.693/λz
$AUC_{(0-t)}$ (µg·h/mL)	Area under the plasma concentration-time curve from time zero to the last measurable timepoint calculated by log-linear trapezoidal summation
$AUC_{(0-\tau)}$ (µg·h/mL)	Area under the plasma concentration-time curve from time zero to dosing interval (tau) postdose at steady state; calculated by log-linear trapezoidal summation
$AUC_{(0-inf)}$(µg·h/mL)	Area under the plasma concentration-time curve from time zero to infinity after single dose; calculated by log-linear trapezoidal summation
CL/F (L/hr)	Apparent clearance after oral administration
Ro	Observed accumulation ratio determined by $AUC_{(0-\tau),ss}$ /$AUC_{(0-24),\ Day\ 1}$

The BGB-10188, zanubrutinib and tislelizumab PK concentration data collected sparsely at predose and postdose (around time to the maximum observed plasma concentration [T_{max}]) will

be tabulated and summarized by visit/cycle. Descriptive statistics will include means, standard deviations, medians, and ranges as appropriate.

Population PK analyses may be conducted as appropriate, and the results of such analysis may be reported separately from the clinical study report.

9.7. Other Analyses

9.7.1. Related PK Analyses

If data permits, correlation between BGB-10188 concentration and corrected QTcF intervals will be assessed to analyze the cardiovascular impact of BGB-10188.

9.7.2. Immunogenicity Analyses

Samples to assess anti-tislelizumab-antibodies will be collected only in patients who receive study drug(s) and at sites that are able to adequately perform sampling, handling, and processing as outlined in the laboratory manual.

The ADA results will be summarized using descriptive statistics by the number and percentage of patients who develop detectable ADAs. The incidence 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.

9.8. Determination of Sample Size

For the dose escalation phase of the study, the number of dose levels examined, the dose escalation cohort size, and the emerging toxicities of the therapy will determine the sample size. A cohort of approximately 3 patients in the dose escalation step will be enrolled and administered at the dose level recommended for the cohort.

Approximately 5 dose levels will be tested for the dose escalation path of BGB-10188 monotherapy in Part A. A total of approximately 30 patients are expected to be enrolled for the BGB-10188 monotherapy dose escalation. The doses of BGB-10188 for the combination therapy in Part B with zanubrutinib 160 mg twice daily will be the latest cleared dose in Part A and subsequent higher dose levels from monotherapy dose escalation. Therefore, a total of approximately 18 patients are expected to be enrolled for the combination therapy dose escalation.

Approximately 6 dose levels of BGB-10188 will be tested for combination therapy dose escalation with tislelizumab 200 mg once every 3 weeks in Part D. A total of approximately 36 patients are expected to be enrolled.

The total sample size in Part A, Part B, and Part D is expected to be approximately 84, excluding patients for the China verification parts. Part C was planned to have approximately 20 patients but will not be initiated. Part E is expected to have approximately 30 to 50 patients. In Part E, patients will be randomized at a 2:1 ratio to receive either BGB-10188 160 mg once daily plus tislelizumab 200 mg once every 3 weeks or BGB-10188 320 mg once daily plus tislelizumab 200 mg once every 3 weeks. No formal hypothesis testing will be performed in the efficacy evaluation. Table 16 shows the two-sided 95% CI for ORR with 10/20/30 patients for different

observed response rates based on the Clopper-Pearson method. The sample size for China verification parts will be based on the escalation status in Part A and Part D.

Table 16: Two-Sided 95% Confidence Interval for ORR With 10/20/30 Patients

Number of Observed Responders/Number of Patients	ORR Estimates	95% CI of ORR
1/10	10%	(0.3%, 44.5%)
2/10	20%	(2.5%, 55.6%)
3/10	30%	(6.7%, 65.2%)
4/10	40%	(12.2%, 73.8%)
2/20	10%	(1.2%, 31.7%)
4/20	20%	(5.7%, 43.7%)
6/20	30%	(11.9%, 54.3%)
8/20	40%	(19.1%, 63.9%)
3/30	10%	(2.1%, 26.5%)
6/30	20%	(7.7%, 38.6%)
9/30	30%	(14.7%, 49.4%)
12/30	40%	(22.7%, 59.4%)

Abbreviations: ORR, overall response rate.

10. STUDY COMMITTEES AND COMMUNICATION

10.1. Safety Monitoring Committee

An SMC will be established and include both the sponsor (including the medical monitor and study team members from Pharmacovigilance/Drug Safety, Clinical Pharmacology, and Biostatistics with other members as appropriate) and investigators. The SMC will review all available safety, efficacy, PK, and exploratory data and make recommendations on dose escalation, dose modification, and dose selection throughout the study. The SMC may also be called upon by the sponsor on an ad hoc basis where applicable to the conduct of the study. A separate charter will outline the details for the composition and responsibility of the SMC.

Part A and Part D (Dose Verification in China)

For the patients in China who receive BGB-10188 as monotherapy or in combination with tislelizumab in the dose-verification study, the SMC will review all the safety data (including AEs and laboratory assessments) and recommend the RDFE before patients join Part B and Part E.

Part E

An SMC meeting will be scheduled once approximately 12 patients have been randomized and have completed at least 1 month of follow-up, or after the first 10 patients are evaluable for efficacy assessment. The SMC will review all available safety and efficacy data and make recommendations on whether the study should continue. Ad hoc meetings can be requested by the SMC if any specific safety concern arises.

11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

The investigator must maintain adequate and accurate records to ensure that the conduct of the study may be fully documented. Such records include but are not limited to the protocol, protocol amendments, ICFs, and documentation of IRB/IEC and governmental approvals. In addition, at the end of the study, the investigator will receive patient data, which will include an audit trail containing a complete record of all changes to such data.

11.1. Access to Information for Monitoring

In accordance with ICH GCP guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the eCRFs for consistency.

The monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any patient records needed to verify the entries on the eCRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected during these monitoring visits are resolved.

11.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of BeiGene may conduct inspections or audits any time during or after completion of this clinical study. If the investigator is notified of an inspection by a regulatory authority, the investigator agrees to notify the sponsor or its designee immediately. The investigator agrees to provide to representatives of a regulatory agency or BeiGene access to records, facilities, and personnel for the effective conduct of any inspection or audit.

12. QUALITY ASSURANCE AND QUALITY CONTROL

12.1. 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 or file the protocol to the appropriate regulatory agency before the study is initiated at a study center in that country.

12.2. Quality Assurance

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.

12.3. Study Site Inspections

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures, working practice documents, and applicable regulations and guidelines. Site audits may be performed periodically by the sponsor's or the contract research organization's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

Site visits will be conducted by the sponsor or an authorized representative to inspect study data, patients' medical records, and eCRFs. The investigator is to permit national and local health authorities; sponsor study monitors, representatives, and collaborators; and IRB/IEC members to inspect all facilities and records relevant to this study.

12.4. Drug Accountability

The investigator or designee (ie, pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient drug dispensation records, and returned or destroyed study product. Dispensation records will document quantities received from BeiGene's designated depot or its designee and quantities dispensed to patients, including batch/lot number, date dispensed, patient identifier number, patient initials, and the initials of the person dispensing the medication.

At study initiation, the monitor will evaluate the site's standard operating procedure for study drug disposal/destruction to ensure that it complies with BeiGene' requirements specified in the Pharmacy Manual. At appropriate times during the conduct of the study or at the end of the study, the study site will dispose of and/or destroy all unused study drug supplies following drug inventory reconciliation by the monitor. These including empty containers, according to these procedures. If the site cannot meet BeiGene's requirements specified in the Pharmacy Manual for disposal, arrangements will be made between the site and BeiGene or its representative for destruction or return of unused study drug supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

13. ETHICS/PROTECTION OF HUMAN PATIENTS

13.1. Ethical Standard

This study will be conducted by the principal investigator and the study center in full conformance with the ICH E6 guideline for GCP and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

13.2. Institutional Review Board/Independent Ethics Committee

This protocol, the ICFs, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/IEC by the principal investigator and reviewed and approved by the IRB/IEC before the study is initiated. In addition, all patient recruitment materials must be approved by the IRB/IEC.

The principal investigator is responsible for providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC. Investigators are also responsible for promptly informing the IRB/IEC of any protocol amendments. In addition to the requirements for reporting all AEs to the sponsor, investigators must comply with requirements for reporting SAEs to the local health authority and IRB/IEC. Investigators may receive written investigational new drug safety reports or other safety-related communications from the sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/IEC and archived in the site's study file.

13.2.1. Protocol Amendments

Any protocol amendments will be prepared by the sponsor. All protocol modifications must be submitted to competent authorities according to local requirements and to the IRB/IEC together with, if applicable, a revised model ICF in accordance with local requirements. Written documentation from competent authorities (according to local requirements) and from the IRB/IEC and required site approval must be obtained by the sponsor before changes can be implemented, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (eg, change in sponsor medical monitor or contact information).

Information on any change in risk and/or change in scope must be provided to patients already actively participating in the study, and the patients must read, understand, and sign each revised ICF confirming their willingness to remain in the study.

13.3. Informed Consent

The sponsor's sample ICF will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The final IRB/IEC-approved ICFs must be provided to the sponsor for health authority submission purposes according to local requirements.

The ICFs must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The ICFs will be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/IEC-approved consent forms must be provided to the sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the ICFs (or to a significant new information/findings addendum in accordance with applicable laws and IRB/IEC policy) during their participation in the study. For any updated or revised ICFs, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised ICFs for continued participation in the study.

A copy of each signed ICF must be provided to the patient or the patient's legally authorized representative. All signed and dated ICFs must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

13.4. Patient and Data Confidentiality

The investigator, institution, sponsor, and site will maintain confidentiality and privacy standards for the collection, storage, transmission, and processing of patients' personal and medical information by following applicable laws and regulations related to the confidentiality, use, and protection of such information, including the ICH GCP Guideline, as implemented locally. Such laws may be more stringent than the requirements in this protocol.

The investigator and site shall code the personal and medical information obtained during the study with a unique patient identification number assigned to each patient enrolled in the study. The investigator must ensure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Unless required to be provided by laws or regulations or specifically requested in exceptional circumstances by the sponsor or its representatives, the investigator and site must ensure that any personal and medical information transmitted to the sponsor or its service providers is: 1) required by the protocol, and 2) appropriately de-identified (eg, via redaction and/or coding with the patient identification number) to ensure the following information about patients are NOT shared:

- names or initials (full or partial);
- full dates of birth;
- contact information (such as phone numbers or home or email addresses);

- numerical identifiers (eg, hospital or medical record, government, health insurance, or financial account numbers) other than patient identification numbers assigned as part of this study;
- geographic identifiers smaller than a state, province, or local equivalent (such as city, county, zip code, or other equivalent geographic identifiers); or
- information about marital status, family, or household members; employment, sex life, sexual preference, or other sensitive data that is not relevant to the study.

Patient personal and medical information obtained during this study is confidential and may only be disclosed to third parties as permitted by the signed ICF (or a separate authorization for the use and disclosure of personal health information that has been signed by the patient), unless permitted or required by law.

In limited circumstances, such as in connection with insurance purposes or patient support services ancillary to certain study sites (eg, for patient travel or reimbursement), the investigator and site may provide certain of this personal information to the sponsor or its representatives. Such personal information may not be provided as part of the study protocol (eg, as part of the eCRF, on samples or reports submitted to the central lab, on safety reporting forms [except in China], or on product dispensing logs provided to the sponsor, etc).

Investigator and site must use only the specific forms and clinical trial systems, (eg, the electronic data capture [EDC] system and any secure file transfer platforms [SFTPs]) designated by the sponsor for sharing and transfers of personal and medical information.

In the event of a breach of the confidentiality of a patient's personal and medical information, the investigator, site, and sponsor, as appropriate, shall fulfill all mediation steps and reporting obligations under applicable laws. If the sponsor identifies personal or medical information that was not properly de-identified, it may be required to report the disclosure under local applicable laws.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare for treatment purposes where allowed by local law or the patient's signed ICF.

Information generated during this study must be available for inspection upon request by representatives of the US FDA, the China NMPA, and all other national and local health authorities; by sponsor monitors, representatives, and collaborators; and by the IRBs/IECs for each study site, as appropriate.

The investigator agrees that all information received from the sponsor, including but not limited to the Investigator's Brochure, this protocol, eCRFs, the investigational drugs, and any other study information, are confidential and remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The investigator further agrees

to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

If a written contract for the conduct of the study that includes confidentiality or privacy provisions inconsistent with this section is executed, that contract's provisions shall apply to the extent they are inconsistent with this section.

13.5. Financial Disclosure

Investigators are required to provide the sponsor with sufficient accurate financial information in accordance with regulations to allow the sponsor to submit complete disclosure or certification to the absence of certain financial interest of the clinical investigators and/or disclose those financial interests, as required to the appropriate health authorities. This is intended to ensure financial interests and arrangements of the clinical investigators with BeiGene that could affect reliability of data submitted to health authorities are identified and disclosed by the sponsor. Investigators are responsible for providing information about their financial interests before participation in the study and to update this information if any relevant changes occur during the study and for 1 year after completion of the study (ie, last patient, last visit).

14. DATA HANDLING AND RECORD KEEPING

14.1. Data Collection and Management Responsibilities

14.1.1. Data Collection

Data required by the protocol will be entered into an EDC system.

Data collection in the eCRF should follow the instructions described in the eCRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered in the eCRF. The investigator or designee must provide e-signature in the EDC system to attest to its accuracy, authenticity, and completeness.

Data contained in the eCRFs are the sole property of BeiGene and should not be made available in any form to third parties without written permission from BeiGene, except for authorized representatives of BeiGene or appropriate regulatory authorities.

14.1.2. Data Management/Coding

At the end of the study, all final patient data, both eCRF and external data (eg, laboratory data), that were collected according to the protocol will be stored by BeiGene or will be properly stored or handled in accordance with applicable laws and regulations.

Standard procedures (including following data review guidelines, computerized validation to produce queries and maintenance of an audit file that includes all database modifications) will be followed to support accurate data collection. Data will be reviewed for outliers, logic, data inconsistencies, and completeness.

During the study, a study monitor (clinical research associate) will make site visits to review protocol compliance, compare eCRFs against individual patient's medical records, and ensure that the study is being conducted according to pertinent regulatory requirements.

The eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained. Checking the eCRFs for completeness and clarity and cross-checking with source documents is required to monitor the progress of the study. Direct access to source data is also required for inspections and audits and will be carried out with due consideration given to data protection and medical confidentiality.

AEs will be coded using MedDRA. Concomitant medications will be coded using the WHO Drug Dictionary. Concomitant diseases/medical history will be coded using MedDRA.

14.2. Study Records Retention

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into ≥ 1 the following categories: 1) investigator's study file, and/or 2) patient clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRF and query forms, IRB/IEC- and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Patient clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the eCRFs) would include documents such as (although not be limited to) the following: patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, electroencephalogram, X-ray, pathology and special assessment reports, consultant letters, screening and enrollment log, etc.

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 ensure 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 backup 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 10 years or as allowed by IRB/IEC.

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

If the investigator cannot guarantee this archiving requirement at the study site for any or all the documents, special arrangements must be made between the investigator and BeiGene to store these in sealed containers outside of the site so that the documents can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the site.

14.3. Protocol Deviations

The investigator is responsible for ensuring that the study is conducted in accordance with the procedures and evaluations described in this protocol. Investigators assert that they will apply due diligence to avoid protocol deviations.

The investigator is to document and explain any deviations from the approved protocol. The investigator must promptly report any major deviations that might impact patient safety and/or data integrity to the sponsor and to the IRB/IEC, in accordance with established IRB/IEC policies and procedures.

14.4. Publication and Data-Sharing 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 ICH Guideline for Structure and Content of Clinical Study Reports (ICH 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 regulatory guidance, and the need to protect the intellectual property of BeiGene (sponsor), regardless of the outcome of the study. The data generated in this clinical study are the exclusive property of the sponsor and are confidential. For multicenter studies, 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 2016).

After conclusion of the study and without prior written approval from BeiGene, investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of BeiGene in an abstract, manuscript, or presentation form; or
- The study has been completed at all study sites for ≥ 2 years.
- No such communication, presentation, or publication will include BeiGene's confidential information.
- Each investigator agrees to submit all manuscripts or congress abstracts and posters/presentations to the sponsor prior to submission. This allows the sponsors 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. The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this trial will be presented in the investigator's clinical study agreement.

14.5. Study and Study Center Closure

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
- Resolution and closure of all data queries
- Accountability, reconciliation, and arrangements for unused study drug(s)

- 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 suspend the enrollment 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 that 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 the return of all unused study drug(s) in accordance with the applicable sponsor procedures for the study.

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

14.6. Information Disclosure and Inventions

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 patient's medical records) are the sole property of the sponsor and 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 to provide appropriate medical care to a patient

- Study results that may be published as described in Section 14.4

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.

15. REFERENCES

American Cancer Society. Caring for the patient with cancer at home: a guide for patients and families. Accessed 2013. www. cancer.org/acs/groups/cid/documents/webcontent/002818-pdf.pdf

Ali K, Soond DR, Pineiro R, et al. Inactivation of PI(3)K p110δ breaks regulatory T-cell-mediated immune tolerance to cancer. Nature. 2014;510(7505):407-11.

Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2018;36(17):1714-68.

Bray F, Ferlay J, Soerjomataram I, et al. Global Cancer Statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;0:1-3.

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics. 1982;38(1):29-41.

Brown JR, Byrd JC, Coutre SE, et al. Idelalisib, an inhibitor of phosphatidylinositol 3-kinase p110d, for relapsed / refractory chronic lymphocytic leukemia. Blood. 2014;123(22):3390-7.

Bruno Bockorny. Botensilimab, a Novel Innate/Adaptive Immune Activator, plus Balstilimab (Anti-PD-1) in Patients with Recurrent Platinum Refractory/Resistant Ovarian Cancer (NCT03860272). 2023 SGO Annual Meeting. Accessed March 26, 2023. https://agenusbio.com/wp-content/uploads/2023/03/26Mar2023_SGO_FINAL.pdf

BRUKINSA™ (zanubrutinib) [US prescribing information]. BeiGene, Inc; 2019.

Cheson BD, Byrd JC, Rai KR, et al. Novel targeted agents and the need to refine clinical endpoints in chronic lymphocytic leukemia. J Clin Oncol. 2012;30(23):2820-2.

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059-68.

Clinical Trials Facilitation Group (CTFG). Recommendations related to contraception and pregnancy testing in clinical trials. Accessed September 15, 2014. http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

Coutré SE, Barrientos JC, Brown JR, et al. Management of adverse events associated with idelalisib treatment: expert panel opinion. Leuk Lymphoma. 2015;56(10):2779-86.

Cull G, Simpson D, Opat S, et al. Treatment with the Bruton tyrosine kinase inhibitor zanubrutinib (BGB-3111) demonstrates high overall response rate and durable responses in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): updated results from a Phase 1/2 trial. Oral presentation at the 61st American Society of Hematology Annual Meeting; December 5-10, 2019; Orlando, FL.

Dolgin M, Association NYH. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. Lippincott Williams and Wilkins; March 1, 1994.

Dreyling M, Santoro A, Mollica L, et al. Copanlisib in patients with relapsed or refractory indolent B-cell lymphoma: Primary results of the pivotal Chronos-1 study [Abstract CT149]. Cancer Res. 2017;77(suppl 13).

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

Flinn IW, Hillmen P, Montillo M, et al. The phase 3 DUO trial: duvelisib vs ofatumumab in relapsed and refractory CLL/SLL. Blood. 2018;132(23):2446-55.

Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. N Engl J Med. 2014;370(11):997-1007.

Haanen JBAG, Carbonnel F, Robert C, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. Ann Oncol. 2017:28 (suppl 4):iv119-iv142.

Hallek M, Cheson BD, Catosvsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood. 2018;131(25):2745-60.

Hamanishi J, Mandai M, Ikeda T, et al. Safety and Antitumor Activity of Anti-PD-1 Antibody, Nivolumab, in Patients With Platinum-Resistant Ovarian Cancer. J Clin Oncol. 2015;33(34):4015-22.

Hanlon A, Brander DM. Managing toxicities of phosphatidylinositol-3-kinase (PI3K) inhibitors. Hematology Am Soc Hematol Educ Program. 2020;2020(1):346-56.

Hao D, Liu J, Chen M, et al. Immunogenomic Analyses of Advanced Serous Ovarian Cancer Reveal Immune Score is a Strong Prognostic Factor and an Indicator of Chemosensitivity. Clin Cancer Res. 2018;24(15):3560-71.

International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. 2016. Accessed 08 August 2017. http://www.icmje.org

Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. New York: John Wiley & Sons; 1980.

KEYTRUDA (pembrolizumab) [US prescribing information]. Merck; 2023.

Kirkwood JM, Iannotti N, Cho D, et al. Effect of JAK/STAT or PI3Kδ plus PD-1 inhibition on the tumor microenvironment: Biomarker results from a Phase 1b study in patients with advanced solid tumors. Cancer Res. 2018;78(13_suppl):CT176.

Koren E, Smith HW, Shores E, et al. Recommendations on risk-based strategies for detection and characterization of antibodies against biotechnology products. J Immunol Methods. 2008;333(1-2):1-9.

Krause G, Hassenruck F, Hallek M. Copanlisib for treatment of B-cell malignancies: the development of a PI3K inhibitor with considerable differences to idelalisib. Drug Des Devel Ther. 2018;12:2577-90.

Kryvenko ON. Do clear cell papillary renal cell carcinomas have malignant potential? Diolombi ML, Cheng L, Argani P, Epstein JI.Am J Surg Pathol. December 2015;39(12):1621-1634. Urol Oncol. 2017;35(6):451-2.

Labrijn AF, Buijsse AO, van den Bremer ET, et al. Therapeutic IgG4 antibodies engage in Fab-arm exchange with endogenous human IgG4 in vivo. Nat Biotechnol. 2009;27(8):767-71.

Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.

Lim EL, Okkenhaug K. Phosphoinositide 3-kinaseδ is a regulatory T-cell target in cancer immunotherapy. Immunology. 2019;157(3):210-8.

Lucas CL, Chandra A, Nejentsev S, et al. PI3Kδ and primary immunodeficiencies. Nat Rev Immunol. 2016;16(11):702-14.

Lynch RC, Paneesha S, Avigdor A, et al. Phase 2 study evaluating the efficacy and safety of parsaclisib in patients with relapsed or refractory follicular lymphoma (CITADEL-203) [ASH Abstract 2935]. 2020.

Matulonis UA, Shapira-Frommer R, Santin AD, et al. Antitumor activity and safety of pembrolizumab in patients with advanced recurrent ovarian cancer: results from the phase II KEYNOTE-100 study. Ann Oncol. 2019;30(7):1080-7.

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

National Cancer Institute. Common Terminology Criteria for Adverse Events Version 5.0. Cancer Therapy Evaluation Program.. Accessed November 27 2017. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

National Cancer Institute. Managing chemotherapy side effects: diarrhea. Accessed 2012. www.cancer.gov/cancertopics/coping/ chemo-side-effects/diarrhea.pdf

Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. Stat Med. 2008;27(13):2420-39.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55.

Okkenhaug K, Fruman DA. PI3Ks in lymphocyte signaling and development. Curr Top Microbiol Immunol. 2010;346:57-85.

Okkenhaug K, Burger JA. PI3K signaling in normal B cells and chronic lymphocytic leukemia (CLL). Curr Top Microbiol Immunol. 2016;393:123-42.

Okkenhaug K, Vanhaesebroeck B. PI3K in lymphocyte development, differentiation and activation. Nat Rev Immunol. 2003;3(4):317-30.

Oliver AJ, Lau PKH, Unsworth AS, et al. Tissue-Dependent Tumor Microenvironments and Their Impact on Immunotherapy Responses. Front Immunol. 2018;9:70.

Patton DT, Garden OA, Pearce WP, et al. Cutting edge: the phosphoinositide 3-kinase p110 delta is critical for the function of CD4+CD25+Foxp3+ regulatory T cells. J Immunol. 2006;177(10):6598-602.

Puri KD, Gold MR. Selective inhibitors of phosphoinositide 3-kinase delta: modulators of B-cell function with potential for treating autoimmune inflammatory diseases and B-cell malignancies. Front Immunol. 2012;3:256.

Riley JL. PD-1 signaling in primary T cells. Immunol Rev. 2009;229(1):114-25.

Rosenberg AS, Worobec A. A risk-based approach to immunogenicity concerns of therapeutic protein products, part 1: considering consequences of the immune response to a protein. BioPharm Intl. 2004a;17(11).

Rosenberg AS, Worobec A. A risk-based approach to immunogenicity concerns of therapeutic protein products, part 2: considering host-specific and product-specific factors impacting immunogenicity. BioPharm Intl. 2004b;17(12).

Soar J, Pumphrey R, Cant A, et al. Emergency treatment of anaphylactic reactions--guidelines for healthcare providers. Resuscitation. 2008;77(2):157-69.

Stockler MR, Hilpert F, Friedlander M, et al. Patient-reported outcome results from the open-label phase III AURELIA trial evaluating bevacizumab-containing therapy for platinum-resistant ovarian cancer. J Clin Oncol. 2014;32(13):1309-16.

Tam CS, Wang M, Simpson D, et al. Updated safety and efficacy data in the Phase 1/2 trial of zanubrutinib in patients with mantle cell lymphoma. Poster presentation at the International Conference on Malignant Lymphoma (ICML); June 18-22, 2019a; Lugano, Switzerland. Abstract 191.

Tam CS, Simpson D, Opat S, et al. Safety and activity of the highly specific BTK inhibitor zanubrutinib (BGB-3111) in patients with indolent and aggressive non-Hodgkin's lymphoma. Oral presentation at the 61st American Society of Hematology Annual Meeting; December 5-10, 2019b; Orlando, FL.

TEVIMBRA™ (tislelizumab) [US prescribing information]. BeiGene, Inc; 2024.

Tighiouart M, Piantadosi S, Rogatko A. Dose finding with drug combinations in cancer phase I clinical trials using conditional escalation with overdose control. Stat Med. 2014;33(22):3815-29.

Trotman J, Opat S, Marlton P, et al. Updated safety and efficacy data from a cohort of patients with Waldenström macroglobulinemia in a Phase 1/2 trial treated with Bruton tyrosine kinase inhibitor zanubrutinib (BGB-3111). Poster presentation at the annual meeting of the European Hematology Association (EHA); June 13-16, 2019; Amsterdam, NL. Abstract PF481.

Wang HQ, Jiang WQ, Li S, et al. Safety and efficacy of TQ-B3525, a novel and selective oral PI3K α/δ inhibitor, in Chinese patients with advanced malignancies: A phase I dose escalation and expansion trial. J Clin Oncol. 2020;38(suppl 15):8058.

Yang Q, Modi P, Newcomb T, et al. Idelalisib: First-in-class PI3K delta inhibitor for the treatment of chronic lymphocytic leukemia, small lymphocytic leukemia, and follicular lymphoma. Clin Cancer Res. 2015;21(7):1537-42.

Yingli Pharma. Yingli Pharma announce promising topline results of a Phase II registration study for treatment of relapsed/refractory follicular lymphoma with the once daily oral PI3Kδ inhibitor, linperlisib. Accessed 19 July 2021. http://www.prnewswire.com/news-releases/yingli-pharma-announce-promising-topline-results-of-a-phase-ii-registration-study-for-treatment-of-relapsedrefractory-follicular-lymphoma-with-the-once-daily-oral-pi3k-inhibitor-linperlisib-301260322.html

Zelenetz AD, Jagadeesh D, Reddy NM, et al. Results of the PI3Kδ inhibitor ME-401 alone or with rituximab in relapsed/refractory (R/R) follicular lymphoma (FL). J Clin Oncol. 2019;37(suppl 15):7512.

Zheng Z, Gao YH, Song YP, et al. Efficacy and safety of duvelisib, a phosphoinositide 3 kinase (PI3K) δ and γ inhibitor, in Chinese patients (pts) with relapsed/refractory follicular lymphoma (R/R FL): A single-arm, open-label, multicenter, phase II clinical trial. J Clin Oncol. 2021;39(suppl 15):e19532.

Zhu Q, Wu X, Wu Y, et al. Interaction between Treg cells and tumor-associated macrophages in the tumor microenvironment of epithelial ovarian cancer. Oncol Rep. 2016;36(6):3472-8.

Zydelig® [US prescribing information]. Gilead Sciences, Inc; 2022.

APPENDIX 1. PART A AND PART B SCHEDULE OF ASSESSMENTS

	Screening [a] -35 to -8 (Part A) -28 to -1 (Part B)	PK Washout [b] -7 to -1	Treatment Period (1 Cycle = 28 Days)							EOT [c]	Safety Follow-up [d]
			Cycle 1				Cycle 2		Cycle 3 and Beyond		
Day		**-7**	**1**	**8**	**15**	**22**	**1**	**15**	**1**	**≤ 7 Days After Stopping Treatment**	**30 Days After Last Dose**
Window (Day)			**-**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**		**± 7**
Informed consent [e]	x										
Inclusion/exclusion criteria	x										
Demographic data	x										
Medical history/baseline conditions	x										
Vital signs	x	x	x	x	x	x	x	x	x	x	x
B-symptoms [f]	x		x				x	x	x	x	
Complete physical examination and weight (height at Screening only) [g]	x										
Targeted PE [g]		x	x	x	x	x	x	x	x	x	x
ECOG Performance Status	x		x	x	x	x	x	x	x	x	x
Echocardiogram or multigated acquisition scan	x										
12-lead ECG [h]	x	x	x		x		x		x	x	
BGB-10188 administration		x	Once daily								
Zanubrutinib administration			Twice daily (only for Part B and patients with disease progression in Part A)								
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x
Adverse events/serious adverse events	x	x	x	x	x	x	x	x	x	x	x
Tumor imaging [i]	x		Every 8 weeks for the first 24 weeks, every 12 weeks for the next 24 weeks, and then every 16 weeks (± 7 days)							x	
Bone marrow aspiration or biopsy [j]	x		At time of CR								
Endoscopy [k]	x		At time of CR								

	Screening [a] -35 to -8 (Part A) -28 to -1 (Part B)	PK Washout [b] -7 to -1	Treatment Period (1 Cycle = 28 Days)							EOT [c]	Safety Follow-up [d]
			Cycle 1				Cycle 2		Cycle 3 and Beyond		
Day		-7	1	8	15	22	1	15	1	≤ 7 Days After Stopping Treatment	30 Days After Last Dose
Window (Day)			-	± 3	± 3	± 3	± 3	± 3	± 3		± 7
Laboratory Tests [l]											
Hematology	x		x	x	x	x	x	x	x	x	
Clinical chemistry	x		x	x	x	x	x	x	x	x	
Coagulation	x		x				x		x	x	
Pregnancy test [m]	x		x				x		x		x
Viral serologies [n]	x		As clinically needed								
Cytomegalovirus monitoring	x		x				x		x		x
Urinalysis [o]	x		x	x	x		x	x	x	x	
Quantitative serum immunoglobulins (IgG, IgM, IgA)	x						x		x		
β_2-Microglobulin	x						x		x		
PK/pharmacodynamics blood sampling		See Appendix 5									
Biomarker blood	x		To be collected at time of first response and time of disease progression [p]								
Archival or fresh tumor tissue [q]	x		Optional biopsy at time of relapse								

Abbreviations: CT, computed tomography; CR, complete response; DLBCL, diffuse large B-cell lymphoma; EOT, End of Treatment; FFPE, formalin-fixed paraffin-embedded; FL, follicular lymphoma; HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; Ig, immunoglobulin; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PE, physical examination; PET, positron emission tomography; PK, pharmacokinetics; SLL, small lymphocytic lymphoma

Note: Assessments scheduled on study drug administration days should be performed prior to dosing, unless otherwise specified.

a. Screening period is from 28 days prior to first dose of study drug, during which all criteria should be strictly assessed. In Part A, the first dose of study drug will be on Day -7. In Part B, the first dose of study drug will be on Cycle 1 Day 1.

b. For Part A only, the first dose of BGB-10188 will occur on Day -7, followed by a PK washout period.

c. EOT is defined as end of treatment of zanubrutinib or BGB-10188, whichever is later. The EOT Visit will be conducted within 7 days after treatment discontinuation. If routine laboratory tests (eg, hematology, clinical chemistry, coagulation, and urinalysis) were completed ≤ 7 days before the EOT Visit, these tests do not need to be repeated. A tumor assessment is not required at the EOT Visit if < 6 weeks have passed since the last assessment. If the EOT Visit did not occur until 30 days (± 7 days) or later after the last dose of study drug, the EOT Visit may also be used as the Safety Follow-up Visit.

[d] The safety follow-up should be conducted within 30 days (± 7 days) after the last dose of zanubrutinib or BGB-10188, whichever is later, or before the start of a new anticancer treatment, whichever occurs first. Investigators should also collect the information about new antitumor therapy. If the interval between EOT Visit and Safety Follow-up Visit is < 7 days, the EOT Visit can be delayed and combined with the safety follow-up visit. If EOT visit and safety follow-up visit are combined, then the site should ensure that all assessments for both visits are done, as some assessments are not common between the visits.

[e] This must occur before any study-specific procedures are conducted and may be obtained before the 28-day screening window. Consent must be obtained using the current version of the form approved by the Independent Ethics Committee/Institutional Review Board.

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

[g] Physical examination includes assessments of cardiovascular, respiratory, abdominal, and neurological systems as well as lymph nodes/spleen, skin, oropharynx, and extremities (as detailed in Section 7.5.1). Targeted physical examination should be limited to systems of clinical relevance (ie, cardiovascular, respiratory, lymph nodes, liver, and spleen), and those systems associated with clinical signs/symptoms and should be performed at every visit including Day -7. Weight will be assessed at screening and at every visit.

[h] All ECGs are to be obtained prior to other assessments scheduled at that same time. If this is not possible, then ECGs are to be obtained ≥ 20 minutes following the last procedure performed. The 12-lead ECG will be done in triplicate (2 minutes apart). The calculated QTcF average of 3 ECGs must be ≤ 480 msec for eligibility. Patients should be in a supine position and resting for ≥ 10 minutes before obtaining the ECGs.

[i] Patients in Part A or Part B with non-Hodgkin lymphoma (ie, SLL, MZL, MCL, FL, or DLBCL) will undergo PET/CT imaging at baseline; a separate CT scan of diagnostic quality should be performed in addition to the PET/CT imaging if the PET/CT imaging is not of diagnostic quality. If PET-avid disease is detected, then subsequent tumor assessments should be conducted with PET/CT-based imaging. Patients in Part A or Part B with non-Hodgkin lymphoma without PET-avid disease, as well as patients with CLL, should undergo tumor assessments with CT-based imaging.

[j] Bone marrow biopsy and/or aspirate is required during screening to assess bone marrow involvement of lymphoma. If a patient has had bone marrow examination performed within 90 days prior to first dose of study drug, a repeated bone marrow biopsy/aspirate is not required. Repeat bone marrow biopsy and aspirate are required if imaging results demonstrate a CR in patients with bone marrow involvement of lymphoma at baseline. For patients with DLBCL, if a follow-up biopsy cannot be obtained, a PET scan that clearly documents continued disease clearance may be used in lieu of the repeated biopsy. More details about bone marrow examination refer to Section 7.6.

[k] For patients with MCL, endoscopy may be performed at Screening for patients with gastrointestinal involvement of their disease. Patients who had an endoscopy performed during the screening period, which confirmed gastrointestinal involvement of MCL, will require an endoscopy to confirm CR. If a follow-up biopsy cannot be obtained, a PET scan that clearly documents continued disease clearance maybe used in lieu of the repeated biopsy.

[l] Local laboratory assessments of clinical chemistry, hematology, coagulation, and urinalysis will be conducted as outlined in Section 7.5.4.

[m] Two negative pregnancy tests (including ≥ 1 blood test) must be obtained before initiating therapy. The first test must be performed within 14 days before BGB-10188 therapy and the second test must be ≤ 72 hours before BGB-10188 therapy. Pregnancy tests must be continued every cycle for ≥ 90 days after the last dose of zanubrutinib and/or BGB-10188. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. A patient who has a positive pregnancy test result at any time after the study drug administration will be immediately withdrawn from participation in the study.

[n] Hepatitis B serology includes HBsAg and HBcAb. Patients negative for HBV antibody do not need HBV DNA test by PCR at screening. Patients who are HBsAg negative, HBcAb positive, and HBV DNA negative will undergo viral load measurement (HBV DNA by PCR) monthly. If a patient is being treated prophylactically with antivirals, HBV DNA screening by PCR must be done at least every 90 days. Hepatitis C serology includes HCV antibody. Patients negative for HCV antibody do not need HCV RNA test by PCR at screening. Patients who are HCV antibody positive, but negative for HCV RNA, will undergo viral load testing (HCV RNA by PCR) monthly. Hepatitis B and hepatitis C testing must be conducted in a laboratory able to perform the tests to the required sensitivity (< 20 IU/mL and < 15 IU/mL for hepatitis B and C, respectively). If sites cannot conduct the tests with this sensitivity or the results are not reported with values, then any positive viral load result should lead to withholding of study treatment and initiation of antiviral treatment. The medical monitor should be informed of any suspected hepatitis B or hepatitis C reactivation.

o. Perform urine dipstick, as well as urine microscopy if dipstick is abnormal. If the urine protein is ≥ 2+ in urinalysis or per clinical discretion, collect 24-hour urine sample.

p. For all patients, blood samples will be collected at screening, time of first response, and time of disease progression to assess blood-based biomarkers and their association with response, resistance, and prognosis.

q. If available, archival tumor tissues (FFPE blocks or approximately 10 to 15 unstained slides) will be requested and sent to the central laboratory for analysis of biomarkers potentially associated with clinical responses. In the absence of archival tumor tissues, an optional, fresh biopsy of a tumor lesion at baseline will be requested. Baseline tissue samples collected during screening will be shipped to a central laboratory for biomarker testing after local regulatory approval. This may occur after the start of study treatment if necessary. A biopsy at disease progression is optional to explore mechanisms of resistance. Written informed consent is required prior to fresh tumor biopsies.

APPENDIX 2. PART C SCHEDULE OF ASSESSMENTS

	Screening [a] -28 to -1	**Treatment Period (1 Cycle = 28 Days)**						**EOT [b]**	**Safety Follow-up [c]**	**Survival Follow-up [d]**
		Cycle 1			**Cycle 2**		**Cycle 3 and Beyond**			
Day		**1**	**2 [e]**	**15**	**1**	**15**	**1**	**≤ 7 Days After Stopping Treatment**	**30 Days After Last Dose**	**Every 3 Months**
Window (Day)		**-**	**-**	**± 3**	**± 3**	**± 3**	**± 3**		**± 7**	**± 14**
Informed consent [f]	x									
Inclusion/exclusion criteria	x									
Demographic data	x									
Medical history/baseline conditions	x									
Vital signs	x	x	x	x	x	x	x	x	x	
B-symptoms [g]	x	x			x		x	x		
Complete physical examination and weight (height at Screening only) [h]	x									
Targeted PE[h]		x			x		x	x	x	
ECOG Performance Status	x	x			x		x	x	x	
Echocardiogram or multigated acquisition scan	x									
12-lead ECG [i]	x	x			x		x	x		
BGB-10188 administration		Once daily								
Zanubrutinib administration		Twice daily								
Concomitant medications	x	x	x	x	x	x	x	x	x	
Adverse events/serious adverse events	x	x	x	x	x	x	x	x	x	

	Screening [a]	**Treatment Period (1 Cycle = 28 Days)**						**EOT** [b]	**Safety Follow-up** [c]	**Survival Follow-up** [d]
	-28 to -1	**Cycle 1**			**Cycle 2**		**Cycle 3 and Beyond**			
Day		**1**	**2** [e]	**15**	**1**	**15**	**1**	**≤ 7 Days After Stopping Treatment**	**30 Days After Last Dose**	**Every 3 Months**
Window (Day)		**-**	**-**	**± 3**	**± 3**	**± 3**	**± 3**		**± 7**	**± 14**
Tumor imaging [j]	x	Every 8 weeks for the first 24 weeks, every 12 weeks for the next 24 weeks, and then every 16 weeks (± 7 days)						x		
Bone marrow aspiration or biopsy [k]	x	x [k]								
Endoscopy [l]	x	At time of CR								
Laboratory Tests										
Hematology	x	x			x		x	x		
Clinical chemistry	x	x		x	x	x	x	x		
Coagulation	x	x			x		x	x		
Pregnancy test [m]	x	x			x		x		x	
Viral serologies [n]	x									
Cytomegalovirus monitoring	x	x			x		x		x	
Urinalysis [o]	x	x			x		x	x		
Quantitative serum immunoglobulins (IgG, IgM, IgA)	x				x		x			
β_2-Microglobulin	x				x		x			
PK/pharmacodynamics blood sampling		See Appendix 5								
Biomarker blood [p]	x	To be collected at time of first response and time of disease progression [p]								
Archival or fresh tumor tissue [q]	x	Optional biopsy at time of relapse								
Survival status										x

Abbreviations: CT, computed tomography; CR, complete response; DLBCL, diffuse large B-cell lymphoma; EOT, End-of-Treatment; FFPE, formalin-fixed paraffin-embedded; FL, follicular lymphoma; HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; Ig, immunoglobulin; MCL, mantle cell lymphoma; PE, physical examination; PET, positron emission tomography; PK, pharmacokinetics; QTcF, QT interval corrected with Fridericia's formula

Note: Assessments scheduled on study drug administration days should be performed prior to dosing, unless otherwise specified.

a. Screening period is from 28 days prior to first dose of study drug, during which all criteria should be strictly assessed. In Part C, the first dose of study drug will be on Cycle 1 Day 1.

b. EOT is defined as end of treatment of zanubrutinib or BGB-10188, whichever is later. The EOT Visit will be conducted within 7 days after treatment discontinuation. If routine laboratory tests (eg, hematology, clinical chemistry, coagulation, and urinalysis) were completed ≤ 7 days before the EOT Visit, these tests do not need to be repeated. A tumor assessment is not required at the EOT Visit if < 6 weeks have passed since the last assessment. If the EOT Visit did not occur until 30 days (± 7 days) or later after the last dose of study drug, the EOT Visit may also be used as the Safety Follow-up Visit.

c. The safety follow-up should be conducted within 30 days (± 7 days) after the last dose of zanubrutinib or BGB-10188, whichever is later, or before the start of a new anticancer treatment, whichever occurs first. Investigators should also collect the information about new antitumor therapy. If the interval between EOT visit and safety follow-up visit is less than 7 days, the EOT visit can be delayed and combined with the safety follow-up visit. If EOT visit and safety follow-up visit are combined, then site should ensure that all assessments for both visits are done as some assessments are not common between the visits.

d. All patients will be followed for survival and further anticancer therapy information after discontinuation of study treatment via telephone calls, patient medical records, and/or clinic visits until death, loss to follow-up, withdrawal of consent, or study completion by the sponsor.

e. Cycle 1 Day 2 visit is only for the first 5 patients in Part C.

f. This must occur before any study-specific procedures are conducted and may be obtained before the 28-day screening window. Consent must be obtained using the current version of the form approved by the Independent Ethics Committee/Institutional Review Board.

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

h. Physical examination includes assessments of cardiovascular, respiratory, abdominal, and neurological systems as well as lymph nodes/spleen, skin, oropharynx, and extremities. Targeted physical examination should be limited to systems of clinical relevance (ie, cardiovascular, respiratory, lymph nodes, liver, and spleen), and those systems associated with clinical signs/symptoms. Weight will be assessed at screening and at every visit.

i. All ECGs are to be obtained prior to other assessments scheduled at that same time. If this is not possible, then ECGs are to be obtained ≥ 20 minutes following the last procedure performed. The 12-lead ECG will be done in triplicate (2 minutes apart). The calculated QTcF average of 3 ECGs must be ≤ 480 msec for eligibility. Patients should be in a supine position and resting for ≥ 10 minutes before obtaining the ECGs.

j. Patients with non-Hodgkin lymphoma (ie, MCL, FL, or DLBCL) will undergo PET/CT imaging at baseline; a separate CT scan of diagnostic quality should be performed in addition to the PET/CT imaging if the PET/CT imaging is not of diagnostic quality. If PET-avid disease is detected, then subsequent tumor assessments should be conducted with PET/CT-based imaging. Patients with non-Hodgkin lymphoma without PET-avid disease should undergo tumor assessments with CT-based imaging.

k. Bone marrow biopsy and/or aspirate is required during screening to assess bone marrow involvement of lymphoma. If a patient has had bone marrow examination performed within 90 days prior to first dose of study drug, a repeated bone marrow biopsy/aspirate is not required. Repeat bone marrow biopsy and aspirate are required if imaging results demonstrate a CR in patients with bone marrow involvement of lymphoma at baseline.

l. For patients with MCL, endoscopy may be performed at Screening for patients with gastrointestinal involvement of their disease. Patients who had an endoscopy performed during the screening period, which confirmed gastrointestinal involvement of MCL, will require an endoscopy to confirm CR. If a follow-up biopsy cannot be obtained, a PET scan that clearly documents continued disease clearance maybe used in lieu of the repeated biopsy.

m. Two negative pregnancy tests (including ≥ 1 blood test) must be obtained before initiating therapy. The first test must be performed within 14 days before BGB-10188 therapy and the second test ≤ 72 hours before BGB-10188 therapy. Pregnancy tests must be continued every cycle for ≥ 90 days after the last dose of zanubrutinib and BGB-10188. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. A patient who has a positive pregnancy test result at any time after the study drug administration will be immediately withdrawn from participation in the study.

[n.] Hepatitis B serology includes HBsAg and HBcAb. Patients negative for HBV antibody do not need HBV DNA test by PCR at screening. Patients who are HBsAg negative, HBcAb positive and HBV DNA negative will undergo viral load measurement (HBV DNA by PCR) monthly. If a patient is being treated prophylactically with antivirals, HBV DNA screening by PCR must be done at least every 90 days. Hepatitis C serology includes HCV antibody. Patients negative for HCV antibody do not need HCV RNA test by PCR at screening. Patients who are HCV antibody positive, but negative for HCV RNA, will undergo viral load testing (HCV RNA by PCR) monthly. Hepatitis B and hepatitis C testing must be conducted in a laboratory able to perform the tests to the required sensitivity (< 20 IU/mL and <15 IU/mL for hepatitis B and C, respectively). The medical monitor should be informed of any suspected hepatitis B or hepatitis C reactivation.

[o.] Perform urine dipstick, as well as urine microscopy if dipstick is abnormal. If the urine protein is ≥ 2+ in urinalysis or per clinical discretion, collect 24-hour urine sample.

[p.] For all patients, blood samples will be collected at screening, time of first response, and time of disease progression to assess blood-based biomarker and their association with response, resistance, and prognosis.

[q.] If available, archival tumor tissues (FFPE blocks or approximately 10 to 15 unstained slides) will be requested and sent to the central laboratory for analysis of biomarkers potentially associated with clinical responses. In the absence of archival tumor tissues, an optional, fresh biopsy of a tumor lesion at baseline will be requested. Baseline tissue samples collected during screening will be shipped to a central laboratory for biomarker testing after local regulatory approval. This may occur after the start of study treatment if necessary. A biopsy at disease progression is optional to explore mechanisms of resistance. Written informed consent is required prior to fresh tumor biopsies

APPENDIX 3. PART D SCHEDULE OF ASSESSMENTS

	Screening [a]	Treatment Period											Safety Follow-up [c]		
		Cycle 1 (28 Days)				Cycle 2 (21 Days)			Cycle 3 (21 Days)		≥ Cycle 4 (Every 21 Days)	EOT Visit [b]			
Visit Day	**-28 to -1**	**1**	**8**	**15**	**22**	**1**	**8 (Phone Call) [p]**	**15**	**1**	**8 (Phone Call) [p]**	**1**	**0 to 7 Days**	**+ 30 Days (Visit)**	**+ 60 Days (Phone Call)**	**+ 90 Days (Phone Call)**
Visit Window			**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**		**± 7**	**± 14**	**± 14**
Informed consent	x														
Inclusion/exclusion criteria	x														
Demographics/medical history[d]	x														
Vital signs/height/weight[e]	x	x	x	x	x	x		x	x		x	x	x		
Physical examination[f]	x	x	x	x	x	x		x	x		x	x	x		
ECOG Performance Status	x	x	x	x	x	x		x	x		x	x	x		
Echocardiogram or multigated acquisition scan	x														
12-lead triplicate ECG[g]	x											x	x		
Eye examination, visual acuity test, and optical coherence tomography (or equivalent diagnostic test)[h]	x										Cycle 4 then every 15 weeks (± 7 days)	x[h]	x[h]		
Adverse events[i]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Prior and concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Prior and concomitant procedures	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hematology[j]	x	x	x	x	x	x		x	x		x	x[b]	x		
Clinical chemistry[j]	x	x	x	x	x	x		x	x		x	x[b]	x		
Coagulation parameters[j]	x	x				x			As clinically indicated			x[b]	x		
Urinalysis[j]	x	x				x			x		x	x[b]	x		
CK and CK-MB[k]	x	x	x[k]	x	x	x[k]		x	x[k]		x[k]	x[b]	x		
Pregnancy test[l]	x[l]	x[l]	x[l]			x[l]			x[l]		x[l]	x	x		

	Screening [a]	Treatment Period											Safety Follow-up [c]		
		Cycle 1 (28 Days)				Cycle 2 (21 Days)			Cycle 3 (21 Days)		≥ Cycle 4 (Every 21 Days)	EOT Visit [b]			
Visit Day	**-28 to -1**	**1**	**8**	**15**	**22**	**1**	**8 (Phone Call) [p]**	**15**	**1**	**8 (Phone Call) [p]**	**1**	**0 to 7 Days**	**+ 30 Days (Visit)**	**+ 60 Days (Phone Call)**	**+ 90 Days (Phone Call)**
Visit Window			**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**		**± 7**	**± 14**	**± 14**
Thyroid function[m]	x[m]					x[m]					Even Cycles[n]		x		
Cytomegalovirus monitoring	x	x				x			x		x		x		
HBV/HCV tests[n]	x														
Pulmonary function tests[o]	x	As clinically indicated													
Biomarkers blood	x	At C2D1, time of first response, and at time of confirmed disease progression													
Pharmacokinetics/pharmacodynamics blood sampling		Appendix 5													
Tumor assessment[q]	x	Week 10 and every 9 weeks (± 7 days) thereafter										x[b]			
Archival or fresh tumor tissue[r]	x	After about 3 to 5 weeks of treatment and at time of confirmed disease progression													
BGB-10188[s]		Daily													
Tislelizumab administration[t]			x			x			x		x				
Anti-tislelizumab antibodies		See Appendix 6													

Abbreviations: AE, adverse event; CK, creatine kinase; CK-MB, creatine kinase cardiac isoenzyme; CT, computed tomography; DLCO, carbon monoxide diffusion capacity; EOT, End of Treatment (Visit); FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; HBcAb, hepatitis B core antibody; HbsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; imAE, immune-mediated adverse event; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; SAE, serious adverse event; T3, triiodothyronine; T4, thyroxine; TLCO, transfer factor for carbon monoxide of lung.

a. Written informed consent is required before performing any study-specific procedure. Results of standard-of-care tests or examinations performed before informed consent has been obtained and ≤ 28 days before the first dose of study drug(s) may be used for screening assessments rather than repeating such tests unless otherwise indicated.

b. The EOT Visit is conducted ≤ 7 days after the investigator determines that the patient must permanently discontinue BGB-10188. If routine laboratory tests (eg, hematology, clinical chemistry, coagulation, and urinalysis) were completed ≤ 7 days before the EOT Visit, these tests do not need to be repeated. A tumor assessment is not required at the EOT Visit if < 6 weeks have passed since the last assessment. If the EOT Visit did not occur until 30 days (± 7 days) or later after the last dose of study drug, the EOT Visit may also be used as the Safety Follow-up Visit. If EOT visit and safety follow-up visit are combined then site should ensure that all assessments for both visits are done as some assessments are not common between the visits.

[c.] Patients who permanently discontinue BGB-10188 will be asked to return to the clinic for the Safety Follow-up Visit, which is required to be conducted 30 days (± 7 days) after the last dose of BGB-10188 (whichever is the latest), unless otherwise specified or before the initiation of subsequent anticancer therapy, whichever occurs first. The Safety Follow-up Visit may coincide with the EOT Visit but cannot occur before the EOT Visit.
Telephone contacts with patients should be conducted to assess imAEs and concomitant medications (if appropriate, ie, associated with an imAE or is a subsequent anticancer therapy) at 60 and 90 days (± 14 days) after the last dose of study drug or the initiation of a subsequent anticancer therapy, whichever occurs earlier. If patients report a suspected imAE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated.

[d.] Includes age or year of birth, gender, and self-reported race/ethnicity.

[e.] Height assessment is required only at screening. Vital signs include measurements of temperature (°C), pulse rate, and blood pressure (systolic and diastolic) while the patient is in a seated position after resting for 10 minutes. If coinciding with study drug infusions, the patient's vital signs are required to be recorded within 60 minutes before, during, and 30 minutes after the first infusion of study drug(s). For subsequent infusions, vital signs will be collected within 60 minutes before infusion of each study drug(s), and if clinically indicated, during and 30 minutes after each study drug(s) infusion. Weight will be assessed at screening and at every visit.

[f.] Complete physical examination is required at screening while subsequent visits entail limited, symptom-directed physical examinations (as detailed in Section 7.5.1). 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.

[g.] The triplicate ECG recordings will be performed at the timepoints specified in the table and when clinically indicated. All ECGs are to be obtained prior to other assessments scheduled at that same time. If this is not possible, then ECGs are to be obtained ≥ 20 minutes following the last procedure performed. The patient should rest in supine position for ≥ 10 minutes in the absence of environmental distractions that may induce changes in heart rate (eg, television, radio, conversation, etc) before each ECG collection.

[h.] Eye examination, visual acuity test, and optical coherence tomography (OCT; or equivalent diagnostic test for retinal examination) captured as standard of care prior to obtaining written informed consent and within 28 days of first dose of study drug may be used rather than repeating tests. Eye examination, including visual acuity test and optical coherence tomography (or equivalent diagnostic test), will be assessed by an appropriate specialist at the Screening Visit. Patients treated with tislelizumab will undergo repeat assessments approximately every 15 weeks (± 7 days).

[i.] The AEs and laboratory abnormalities will be graded per NCI-CTCAE Version 5.0. All AEs will also be evaluated for seriousness. After the informed consent form has been signed, but before the administration of study drug(s), only SAEs should be reported to the sponsor. After initiation of study drug(s), all AEs and SAEs, regardless of relationship to study drug(s), will be reported until either 30 days after last dose of study drug(s) or the initiation of subsequent anticancer therapy, whichever occurs first. imAEs (serious or nonserious) should be reported until 90 days after the last dose of study drug or initiation of a subsequent anticancer therapy, whichever occurs earlier.

[j.] Local laboratory assessments of clinical chemistry, hematology, coagulation, and urinalysis will be conducted as outlined in Section 7.5.4. If clinical chemistry, hematology, and coagulation at screening are not performed within 72 hours before the first study drug administration, these tests should be repeated and reviewed before study drug administration. After Day 1 of Cycle 1, results are to be performed and reviewed within 48 hours before study drug administration. Hematology and clinical chemistry will be performed weekly for the first 2 cycles and then on Day 1 only of each subsequent cycle. Coagulation test will be conducted on Day 1 of the first 2 cycles and as clinically indicated at subsequent cycles. Urinalysis test will be conducted on Day 1 of every cycle. If the urine protein ≥ 2+ in urinalysis or per clinical discretion, collect 24-hour urine sample. Refer to Section 7.5.4 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.

[k.] CK and CK-MB levels will be evaluated at the timepoints specified within the table and when clinically indicated. If CK-MB fractionation is not available, troponin I and/or troponin T should be tested instead.

[l.] Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative ≤ 14 days before the first dose of study drug(s). A negative urine pregnancy test must be completed and recorded ≤ 72 hours before the administration of study drug(s) at each cycle. On Cycle 1 Day 8, a negative urine pregnancy test also must be completed and recorded ≤ 72 hours before the administration of tislelizumab. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.

[m.] Analysis of free T3, free T4, and thyroid stimulating hormone will be performed by a central laboratory and/or the local study site laboratory.

[n.] Hepatitis B serology includes HbsAg and HbcAb. Patients negative for HBV antibody do not need HBV DNA test by PCR at screening. Patients who are HbsAg negative, HbcAb positive and HBV DNA negative will undergo viral load measurement (HBV DNA by PCR) monthly. If a patient is being treated prophylactically with antivirals, HBV DNA screening by PCR must be done at least every 90 days. Hepatitis C serology includes HCV antibody. Patients negative for HCV antibody do not need HCV RNA test by PCR at screening. Patients who are HCV antibody positive, but negative for HCV RNA, will undergo viral load testing (HCV RNA by PCR) monthly. Hepatitis B and hepatitis C testing must be conducted in a laboratory able to perform the tests to the required sensitivity (< 20 IU/mL and <15 IU/mL for hepatitis B and C, respectively). If sites cannot conduct the tests with this sensitivity or the results are not reported with values, then any positive viral load result should lead to withholding of study treatment and initiation of antiviral treatment. The medical monitor should be informed of any suspected hepatitis B or hepatitis C reactivation.

[o.] The pulmonary function tests including the measurements of FEV1, FVC, DLCO or TLCO, and so on, will be performed ≤ 4 weeks before the first dose of study drug(s).

[p.] Cycle 3 Day 8 visit may be a telephone visit. The investigator should arrange an unscheduled visit if further assessment is indicated.

[q.] Tumor imaging will be performed ≤ 28 days before the first dose of study drug(s). Results of standard-of-care tests or examinations performed before informed consent has been obtained and ≤ 28 days before the first dose of study drug(s) may be used for the purposes of screening rather than repeating the standard-of-care tests. During the study, tumor imaging will be performed, based on RECIST Version 1.1, at screening and Week 10 then every 9 weeks (±7 days) thereafter until loss of clinical benefit, use of alternative anticancer therapy, withdrawal of consent, death, lost to follow-up, or end of study, whichever occurs first. Tumor assessments must include CT scans (with oral/intravenous contrast, unless contraindicated) or MRI, with preference for CT, of the chest, abdomen, and pelvis. All measurable and evaluable lesions should be assessed and documented at the Screening Visit and reassessed at each subsequent tumor evaluation. The same radiographic procedure used to assess disease sites at screening must be used throughout the study (eg, the same contrast protocol for CT scans).

[r.] Archival or fresh tumor tissue: A fresh tumor biopsy collected at screening is strongly recommended for analysis of biomarkers potentially associated with clinical responses. If a fresh tumor biopsy is not available, an archival tissue sample (either an FFPE block with tumor tissue [preferred] or 10 to 15 unstained slides) is required. It is recommended that the archival tissue sample is collected within 2 years before screening. Baseline tissue samples collected during screening will be shipped to a central laboratory for biomarker testing after local regulatory approval. This may occur after the start of study treatment if necessary. An optional biopsy after approximately 3 to 5 weeks of treatment is also strongly recommended for biomarker analysis. Optional biopsies will also be taken at accessible tumor sites from the patients who have confirmed disease progression during the study for mechanisms of resistance. If feasible, any follow-up biopsy should be ideally taken from the same tumor lesion as the baseline biopsy.

[s.] BGB-10188 will be administered orally daily at the dose designated by predefined dose levels during the 28-day cycle of Cycle 1 and then each 21-day cycle of Cycle 2 and beyond. Patients will receive study drug until they are no longer considered to be achieving clinical benefit, unacceptable toxicity, or withdrawal of informed consent.

[t.] Tislelizumab will be given intravenously on Day 8 of Cycle 1 and Day 1 of each subsequent 21-day cycle (once every 3 weeks) (see Section 5.2.3 for details). Note: Tislelizumab must not be concurrently infused with any other drug. Tislelizumab should be infused ≥ 30 minutes after BGB-10188 administration.

APPENDIX 4. PART E SCHEDULE OF ASSESSMENTS

	Screening [a]	**Treatment Period**				**EOT Visit** [b]	**Safety Follow-up** [c]			**Survival Follow-up** [d] **(Every 3 Months) ± 14 Days**
		Cycle 1 and Cycle 2 (21 Days)			**Cycle 3 and Beyond (21 days)**					
Visit Day	**-28 to -1**	**1**	**8**	**15**	**1**	**0 to 7 Days**	**+ 30 Days (Visit)**	**+ 60 Days (Phone Call)**	**+ 90 Days (Phone Call)**	
Visit Window		**± 3 (C2D1 Only)**	**± 3**	**± 3**	**± 3**		**± 7**	**± 14**	**± 14**	
Informed consent	x									
Inclusion/exclusion criteria	x									
Demographics/medical history[e]	x									
Vital signs/height/weight[f]	x	x			x	x	x			
Physical examination[g]	x	x			x	x	x			
ECOG Performance Status	x	x			x	x	x			
12-lead triplicate ECG[h]	x									
Adverse events[i]	x	x	x	x	x	x	x	x	x	
Prior and concomitant medications	x	x	x	x	x	x	x	x	x	
Prior and concomitant procedures	x	x	x	x	x	x	x	x	x	
Hematology[j]	x	x	x	x	x	x[b]	x			
Clinical chemistry[j]	x	x	x	x	x	x[b]	x			
Coagulation parameters[j]	x	x			As clinically indicated	x[b]	x			

	Screening [a]	**Treatment Period**				**EOT Visit** [b]	**Safety Follow-up** [c]			**Survival Follow-up** [d] **(Every 3 Months) ± 14 Days**
		Cycle 1 and Cycle 2 (21 Days)			**Cycle 3 and Beyond (21 days)**					
Visit Day	**-28 to -1**	**1**	**8**	**15**	**1**	**0 to 7 Days**	**+ 30 Days (Visit)**	**+ 60 Days (Phone Call)**	**+ 90 Days (Phone Call)**	
Visit Window		**± 3 (C2D1 Only)**	**± 3**	**± 3**	**± 3**		**± 7**	**± 14**	**± 14**	
Urinalysis[j]	x	x			As clinically indicated	x[b]	x			
CK and CK-MB[k]	x	x	x	x	x[l]	x[b]	x			
Pregnancy test[l]	x	x			x	x	x			
Thyroid function[m]	x	x (C2D1 only)			Every even cycle		x			
Cytomegalovirus monitoring	x	x			x		x			
HBV/HCV tests[n]	x									
Pulmonary function tests[o]	As clinically indicated									
Biomarkers blood	x	At C2D1, time of first response, and at time of confirmed disease progression								
Pharmacokinetics/ pharmacodynamics blood sampling		See Appendix 5								
Tumor assessment[p]	x	Week 9 and every 9 weeks (± 7 days) thereafter				x[b]				

	Screening [a]	Treatment Period				EOT Visit [b]	Safety Follow-up [c]			Survival Follow-up [d] (Every 3 Months) ± 14 Days
		Cycle 1 and Cycle 2 (21 Days)			Cycle 3 and Beyond (21 days)					
Visit Day	**-28 to -1**	**1**	**8**	**15**	**1**	**0 to 7 Days**	**+ 30 Days (Visit)**	**+ 60 Days (Phone Call)**	**+ 90 Days (Phone Call)**	
Visit Window		**± 3 (C2D1 Only)**	**± 3**	**± 3**	**± 3**		**± 7**	**± 14**	**± 14**	
CA-125[q]	x (-14 to -1)	Week 9 and every 9 weeks (± 7 days) thereafter				x[b]				
Archival or fresh tumor tissue[r]	x	After about 3 to 5 weeks of treatment and at time of confirmed disease progression								
BGB-10188 administration[s]		Daily								
Tislelizumab administration[t]		x			x					
Anti-tislelizumab antibodies		See Appendix 6								
Survival status										x

Abbreviations: AE, adverse event; CA-125, carcinoma antigen-125; CK, creatine kinase; CK-MB, creatine kinase cardiac isoenzyme; CT, computed tomography; DLCO, carbon monoxide diffusion capacity; EOT, End of Treatment (Visit); FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; imAE, immune-mediated adverse event; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; SAE, serious adverse event; T3, triiodothyronine; T4, thyroxine; TLCO, transfer factor for carbon monoxide of lung.

a. Written informed consent is required before performing any study-specific procedure. Results of standard-of-care tests or examinations performed before informed consent which have been obtained ≤ 28 days before the first dose of study drug(s) may be used for screening assessments rather than repeating such tests unless otherwise indicated.

b. The EOT Visit is conducted ≤ 7 days after the investigator determines that the patient must permanently discontinue BGB-10188 and tislelizumab. If routine laboratory tests (eg, hematology, clinical chemistry, coagulation, and urinalysis) were completed ≤ 7 days before the EOT Visit, these tests do not need to be repeated. A tumor assessment (including CA-125 tumor assessment) is not required at the EOT Visit if < 6 weeks have passed since the last assessment. Patients who discontinue study treatment before disease progression will need to undergo tumor assessments as outlined in Section 7.6. If the EOT Visit did not occur until 30 days (± 7 days) or later after the last dose of study drug, the EOT Visit may also be used as the Safety Follow-up Visit. If EOT visit and safety follow-up visit are combined then site should ensure that all assessments for both visits are done as some assessments are not common between the visits.

c. Patients who permanently discontinue BGB-10188 will be asked to return to the clinic for the Safety Follow-up Visit, which is required to be conducted 30 days (± 7 days) after the last dose of BGB-10188 or tislelizumab (whichever is later) unless otherwise specified or before the initiation of subsequent anticancer therapy, whichever occurs first. The Safety Follow-up Visit may coincide with the EOT Visit but cannot occur before the EOT Visit. Telephone contacts with patients should be conducted to assess imAEs and concomitant medications (if appropriate, ie, associated with an imAE or is a subsequent anticancer therapy) at 60 and 90 days (± 14 days) after the last dose of study drug or the initiation of a subsequent anticancer therapy, whichever occurs earlier. If patients report a suspected imAE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated.

d. Survival follow-up information will be collected via telephone calls, email or other communication; patient medical records; and/or clinic visits approximately every 3 months after the EOT/Safety Follow-up Visit or directed by the sponsor until death, loss to follow-up, withdrawal of consent, or study termination by sponsor. Only new anticancer treatment will be collected at Survival Follow-up Visits.

e. Includes age or year of birth, gender, and self-reported race/ethnicity. History of treatment for the primary diagnosis, including prior medication, loco-regional treatment(s), and surgical treatment(s). Pre-existing AEs at baseline should be recorded as medical history.

f. Height assessment is required only at screening. Vital signs include measurements of temperature (°C), pulse rate, and blood pressure (systolic and diastolic) while the patient is in a seated position after resting for 10 minutes. If coinciding with study drug infusions, the patient's vital signs are required to be recorded within 60 minutes before, during, and 30 minutes after the first infusion of study drug(s). For subsequent infusions, vital signs will be collected within 60 minutes before infusion of each study drug(s), and if clinically indicated, during and 30 minutes after each study drug(s) infusion. Weight will be assessed at screening and at every visit.

g. Complete physical examination is required at screening while subsequent visits entail limited, symptom-directed physical examinations (as detailed in Section 7.5.1). 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.

h. The triplicate ECG recordings will be performed at the timepoints specified in the table and when clinically indicated. All ECGs are to be obtained prior to other assessments scheduled at that same time. If this is not possible, then ECGs are to be obtained ≥ 20 minutes following the last procedure performed. The patient should rest in supine position for ≥ 10 minutes in the absence of environmental distractions that may induce changes in heart rate (eg, television, radio, conversation, etc) before each ECG collection.

i. The AEs and laboratory abnormalities will be graded per NCI-CTCAE v5.0. All AEs will also be evaluated for seriousness. After the informed consent form has been signed, but before the administration of study drug(s), only SAEs should be reported to the sponsor. After initiation of study drug(s), all AEs and SAEs, regardless of relationship to study drug(s), will be reported until either 30 days after last dose of study drug(s) or the initiation of subsequent anticancer therapy, whichever occurs first. imAEs (serious or nonserious) should be reported until 90 days after the last dose of study drug or initiation of a subsequent anticancer therapy, whichever occurs earlier.

j. Local laboratory assessments of clinical chemistry, hematology, coagulation, and urinalysis will be conducted as outlined in Section 7.5.4. If clinical chemistry, hematology, and coagulation at Screening are not performed within 72 hours before the first study drug administration, these tests should be repeated and reviewed before study drug administration. After Day 1 of Cycle 1, results are to be performed and reviewed within 48 hours before study drug administration. Hematology and clinical chemistry will be performed weekly for the first 2 cycles and then on Day 1 only of each subsequent cycle. Coagulation test will be conducted on Day 1 of the first 2 cycles and as clinically indicated at subsequent cycles. Urinalysis test will be conducted on Day 1 of every cycle. If the urine protein ≥ 2+ in urinalysis or per clinical discretion, collect 24-hour urine sample. Refer to Section 7.5.4 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.

k. CK and CK-MB levels will be evaluated at the timepoints specified within the table and when clinically indicated. If CK-MB fractionation is not available, troponin I and/or troponin T should be tested instead.

l. Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative ≤ 14 days before the first dose of study drug(s). A negative urine pregnancy test must be completed and recorded ≤ 72 hours before the administration of study drug(s) at each cycle. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.

m. Analysis of free T3, free T4, and thyroid stimulating hormone will be performed by a central laboratory and/or the local study site laboratory.

n. Testing at screening will consist of HBsAg, HBsAb, HBcAb, and HCV antibody. Patients negative for HBV antibody do not need HBV DNA test by PCR at screening. Patients who are HBsAg negative, HBcAb positive and HBV DNA negative will undergo viral load measurement (HBV DNA by PCR) monthly. If a patient is being treated prophylactically with antivirals, HBV DNA screening by PCR must be done at least every 90 days. Patients negative for HCV antibody do not need HCV RNA test by PCR at screening. Patients who are HCV antibody positive, but negative for HCV RNA, will undergo viral load testing (HCV RNA by PCR) monthly. The medical monitor should be informed of any suspected hepatitis B or hepatitis C reactivation.

o. Patients suspected or known to have serious/severe respiratory conditions or who exhibit significant respiratory symptoms unrelated to the underlying cancer or who have a history of thoracic radiotherapy will undergo pulmonary function testing during screening or whenever clinically indicated. The pulmonary function tests including the measurements of FEV1, FVC, DLCO or TLCO, and so on, will be performed ≤ 4 weeks before the first dose of study drug(s).

p. Tumor imaging will be performed ≤ 28 days before the first dose of study drug(s). Results of standard-of-care tests or examinations performed before informed consent has been obtained and ≤ 28 days before the first dose of study drug(s) may be used for the purposes of screening rather than repeating the standard-of-care tests. During the study, tumor imaging will be performed, based on RECIST Version 1.1, at screening, Week 9, and then every 9 weeks (±7 days) thereafter until loss of clinical benefit, use of alternative anticancer therapy, withdrawal of consent, death, lost to follow-up, or end of study, whichever occurs first. Tumor assessments must include CT scans (with oral/intravenous contrast, unless contraindicated) or MRI, with preference for CT, of the chest, abdomen, and pelvis. All measurable and evaluable lesions should be assessed and documented at the Screening Visit and reassessed at each subsequent tumor evaluation. The same radiographic procedure used to assess disease sites at screening must be used throughout the study (eg, the same contrast protocol for CT scans).

q. Patients will have CA-125 tested in local laboratory within 14 days before the first dose of study drug, at Week 9, and then every 9 weeks (±7 days) thereafter until loss of clinical benefit, use of alternative anticancer therapy, withdrawal of consent, death, lost to follow-up, or end of study, whichever occurs first. Patients can be evaluated according to CA-125 only if they have a pretreatment sample that is at least twice the upper limit of the reference range and within 2 weeks before starting the treatment. When there is initial CA-125 response, it is suggested to confirm the response after 28 days (+7 days) after the initial response.

r. Archival or fresh tumor tissue: A fresh tumor biopsy collected at screening is strongly recommended for analysis of biomarkers potentially associated with clinical responses. If a fresh tumor biopsy is not available, an archival tissue sample (either an FFPE block with tumor tissue [preferred] or 10 to 15 unstained slides) is required. It is recommended that the archival tissue sample is collected within 2 years before screening. Baseline tissue samples collected during screening will be shipped to a central laboratory for biomarker testing after local regulatory approval. This may occur after the start of study treatment if necessary. An optional biopsy after approximately 3 to 5 weeks of treatment is also strongly recommended for biomarker analysis. Optional biopsies will also be taken at accessible tumor sites from the patients who have confirmed disease progression during the study for mechanisms of resistance. If feasible, any follow-up biopsy should be ideally taken from the same tumor lesion as the baseline biopsy.

s. BGB-10188 will be administered orally daily at the dose designated by predefined dose levels.

t. Tislelizumab will be given intravenously on Day 1 of each 21-day cycle (once every 3 weeks) (see Section 5.2.3 for details). Note: Tislelizumab must not be concurrently infused with any other drug. Tislelizumab should be infused ≥ 30 minutes after BGB-10188 administration.

APPENDIX 5. SCHEDULE OF PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

Part A BGB-10188 Monotherapy Dose Escalation

Time		PK Washout (D-7 to D1) [a] and C1D15												
Sample		**Predose**	**0.5 h**	**1 h**	**2 h**	**3 h**	**4 h**	**6 h**	**8 h**	**12 [b] h**	**24 [d] h**	**48 h**	**72 h**	**168 h**
	Window Allowed	**-30 min**	**±10 min**	**±10 min**	**±10 min**	**±15 min**	**±15 min**	**±20 min**	**±30 min**	**±1 h**	**±1 h**	**±1 h**	**±1 h**	**±1 h**
All Patients	BGB-10188 - PK (PK washout)	X	X	X	X	X	X	X	X	X	X	X	X	X
	BGB-10188 - PK (C1D15)	X	X	X	X	X	X	X	X	X	X			
	Mealtime	Collect the mealtime within 6 hours postdose												
	BGB-10188 pharmacodynamic (PK washout and C1D15)	X			X									
	ECG [c] **Triplicate per point** (PK washout and C1D15)	X (within -30 min)			X (within -30 min)		X (within -30 min)							

Abbreviation: PK, pharmacokinetics.

Notes: The triplicate ECGs for each patient should be obtained from the same machine whenever possible.

It is important that PK and pharmacodynamic sampling occurs as close as possible to the scheduled time. To achieve this, other assessments at the same time can be advanced or delayed so that there is sufficient time to complete the blood sampling. Thus, the sequence at a particular timepoint is as follows: 1) scheduled ECG; 2) vital sign measurements; 3) PK/pharmacodynamic blood samples (to be performed at the precise protocol scheduled time); and 4) any other scheduled or unscheduled measurements at that timepoint.

[a.] Applies to all dose levels.

[b.] Sampling at 12 hours is optional.

[c.] ECG tests at 2 hours and 4 hours should be paired with related PK sampling.

[d.] 24-hour samples should be collected prior to next dosing.

Part B BGB-10188 + Zanubrutinib Dose Escalation

Time		C1D1 and C1D15									
Sample		Predose	0.5 h	1 h	2 h	3 h	4 h	6 h	8 h	12 [a] h	24 [b] h
	Window Allowed	-30 min	±10 min	±10 min	±10 min	±15 min	±15 min	±20 min	±30 min	±1 h	±1 h
All Patients	BGB-10188--PK	X	X	X	X	X	X	X	X	X	X
	BGB-10188--pharmacodynamic	X			X						
	Zanubrutinib--PK	X	X	X	X	X	X	X	X		

Abbreviation: PK, pharmacokinetics.
It is important that PK and pharmacodynamic sampling occurs as close as possible to the scheduled time. To achieve this, other assessments at the same time can be advanced or delayed so that there is sufficient time to complete the blood sampling.
[a.] Sampling at 12 hours is optional.
[b.] 24-hour samples should be collected prior to next dosing.

Part C BGB-10188 + Zanubrutinib Dose Expansion

Time		C1D1 and C2D1										Day 1 of Cycles 5, 7, 10, and 13	
Sample		Predose	0.5 h	1 h	2 h	3 h	4 h	6 h	8 h	12 [a] h	24 [b] h	Predose	2 h
	Window Allowed	-30 min	±10 min	±10 min	±10 min	±15 min	±15 min	±20 min	±30 min	±1 h	±1 h	-30 min	±10 min
First Patients in Each Cohort	BGB-10188 - PK	X	X	X	X	X	X	X	X	X	X	X	X
	BGB-10188 - pharmacodynamic	X			X								
	Zanubrutinib - PK	X	X	X	X	X	X	X	X				
Remaining Patients	BGB-10188 - PK	X			X							X	X

Abbreviation: PK, pharmacokinetics.
It is important that PK and pharmacodynamic sampling occurs as close as possible to the scheduled time. To achieve this, other assessments at the same time can be advanced or delayed so that there is sufficient time to complete the blood sampling.
[a.] Sampling at 12 hours is optional.
[b.] 24-hour samples should be collected prior to next dosing.

Part D BGB-10188 + Tislelizumab Dose Escalation

Time		C1D1 and C2D1								
Sample		Predose	0.5 h	1 h	2 h	4 h	6 h	8 h	12 [a] h	24 [b] h
	Window Allowed	-30 min	±10 min	±10 min	±10 min	±15 min	±20 min	±30 min	±1 h	±1 h
All patients	BGB-10188 - PK	X	X	X	X	X	X	X	X	X
	BGB-10188 - pharmacodynamic	X			X					
	Mealtime	Collect the mealtime within 6 hours after dosing								

Abbreviation: PK, pharmacokinetics.
It is important that PK and pharmacodynamic sampling occurs as close as possible to the scheduled time. To achieve this, other assessments at the same can be advanced or delayed so that there is sufficient time to complete the blood sampling.
[a.] Sampling at 12 hours is optional.
[b.] 24-hour sample should be collected prior to next dosing.

Part E BGB-10188 + Tislelizumab Dose Expansion

Time		C1D1 and C2D1									Day 1 of Cycles 5 and 9
Sample		Predose	0.5 h	1 h	2 h	4 h	4 to 6 h	6 h	8 h	24 [a] h	Predose
	Window Allowed	-30 min	±10 min	±10 min	±10 min	±15 min		±20 min	±30 min	±1 h	-30 min
Approximately 5 Patients	BGB-10188 - PK	X	X	X	X	X		X	X	X	X
	BGB-10188 - pharmacodynamic	X			X						
Remaining Patients	BGB-10188 - PK	X			X		X				X

Abbreviation: PK, pharmacokinetics.
It is important that PK and pharmacodynamic sampling occurs as close as possible to the scheduled time. To achieve this, other assessments at the same time can be advanced or delayed so that there is sufficient time to complete the blood sampling.
[a.] 24-hour sample should be collected prior to next dosing.

APPENDIX 6. PART D AND PART E SCHEDULE OF PK/ADA ASSESSMENTS

Part D BGB-10188 + Tislelizumab Dose Escalation

Time	Cycle 1 Day 8		Cycle 2 Day 1	Cycle 5 Day 1		Cycle 9 Day 1	Cycle 17 Day 1	EOT/Safety Follow-up Visit
	Pre-infusion	0 h Post-infusion	Pre-infusion	Pre-infusion	0 h Post-infusion	Pre-infusion	Pre-infusion	
Window Allowed	**-1 h**	**+30 min**	**-1 h**	**-1 h**	**+30 min**	**-1 h**	**-1 h**	
Tislelizumab - PK Serum Sample [a]	X	X	X	X	X	X	X	X
Tislelizumab - ADA Serum Sample [b]	X		X	X		X	X	X

Abbreviations: ADA, antidrug antibody; EOT, end of treatment; IEC, Independent Ethics Committee; IRB, Institutional Review Board; PK, pharmacokinetics.

[a.] Should a patient taking tislelizumab present with any Grade 3 or above immune-mediated adverse event, an additional blood PK samples may be taken to determine the serum concentration of tislelizumab. These tests are required when it is allowed by local regulations/IRBs/IECs.

[b.] All samples should be drawn at the same time as blood collection for predose PK samples. These tests are required when it is allowed by local regulations/IRBs/IECs.

Part E BGB-10188 + Tislelizumab Dose Expansion

Time	Cycle 1 Day 1		Cycle 2 Day 1	Cycle 5 Day 1		Cycle 9 Day 1	Cycle 17 Day 1	EOT/Safety Follow-up Visit
	Pre-infusion	0 h Post-infusion	Pre-infusion	Pre-infusion	0 h Post-infusion	Pre-infusion	Pre-infusion	
Window Allowed	**-1 h**	**+30 min**	**-1 h**	**-1 h**	**+30 min**	**-1 h**	**-1 h**	
Tislelizumab - PK Serum Sample [a]	X	X	X	X	X	X	X	X
Tislelizumab - ADA Serum Sample [b]	X		X	X		X	X	X

Abbreviations: ADA, antidrug antibody; EOT, end of treatment; IEC, Independent Ethics Committee; IRB, Institutional Review Board; PK, pharmacokinetics.

[a.] Should a patient taking tislelizumab present with any Grade 3 or above immune-mediated adverse event, an additional blood PK samples may be taken to determine the serum concentration of tislelizumab. These tests are required when it is allowed by local regulations/IRBs/IECs.

[b.] All samples should be drawn at the same time as blood collection for predose PK samples. These tests are required when it is allowed by local regulations/IRBs/IECs.

APPENDIX 7. CONTRACEPTION GUIDELINES AND DEFINITIONS OF "WOMEN OF CHILDBEARING POTENTIAL," "NO CHILDBEARING POTENTIAL"

Contraception Guidelines

The Clinical Trials Facilitation Group recommendations related to contraception and pregnancy testing in clinical trials include the use of highly effective forms of birth control (Clinical Trials Facilitation Group 2014). These methods include the following:

- Combined (estrogen and progestogen containing) hormonal contraception associated with the inhibition of ovulation
  - Oral, intravaginal, or transdermal
- Progestogen-only hormonal contraception associated with the inhibition of ovulation
  - Oral, injectable, implantable
  - Note: Oral birth control pills are not considered a highly effective form of birth control, and if they are selected, they must be used with a second, barrier method of contraception such as condoms with or without spermicide
- An intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
  - Note: This is only considered a highly effective form of birth control when the vasectomized partner is the sole partner of the study participant and there has been a medical assessment confirming surgical success
  - A sterile male is one for whom azoospermia, in a semen sample, has been demonstrated as definitive evidence of infertility
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment). NOTE: Total sexual abstinence should only be used as a contraceptive method if it is in line with the patients' usual and preferred lifestyle. Periodic abstinence (eg, calendar, ovulation, sympto-thermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable methods of contraception.

Of note, barrier contraception (including male and female condoms with or without spermicide) is not considered a highly effective method of contraception and if used, this method must be used in combination with one of the highly effective forms of birth control listed above.

Definitions of "Women of Childbearing Potential" and "Women of No Childbearing Potential"

In this protocol, "women of childbearing potential" are defined as female patients who are physiologically capable of becoming pregnant.

Conversely, "women of no childbearing potential" are defined as female patients meeting any of the following criteria:

- Surgically sterile (ie, through bilateral salpingectomy, bilateral oophorectomy, or hysterectomy)
- Postmenopausal, defined as:
  - ≥ 55 years of age with no spontaneous menses for ≥ 12 months, OR
  - < 55 years of age with no spontaneous menses for ≥ 12 months AND with postmenopausal follicle-stimulating hormone concentration > 30 IU/mL and all alternative medical causes for the lack of spontaneous menses for ≥ 12 months have been ruled out, such as polycystic ovarian syndrome, hyperprolactinemia, etc.

If an follicle-stimulating hormone measurement is required to confirm postmenopausal state, concomitant use of hormonal contraception or hormonal replacement therapy should be excluded.

APPENDIX 8. NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

Class	Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Adapted from Dolgin 1994.
Original source: Criteria Committee, New York Heart Association, Inc. Diseases of the Heart and Blood Vessels. Nomenclature and Criteria for diagnosis, 6th edition Boston, Little, Brown and Co. 1964, p 114.

APPENDIX 9. INFUSION-RELATED REACTIONS, HYPERSENSITIVITY REACTIONS AND IMMUNE-MEDIATED ADVERSE EVENTS: EVALUATION AND MANAGEMENT

Management of Infusion-Related Reactions and Hypersensitivity Reactions

Management and treatment modifications for symptoms of infusion-related reactions associated with study drug(s) administration are provided in the table below.

If a hypersensitivity reaction occurs, the patient must be managed according to the best available medical practice, as described in the guideline for emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (United Kingdom) (Soar et al 2008). Patients should be instructed to report any delayed reactions to the investigator immediately.

Treatment Modifications for Symptoms of Infusion-Related or Hypersensitivity Reactions Associated with Study Drug(s) Administration

NCI-CTCAE Grade	Treatment Modification for Study Drug(s)
Grade 1 - Mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease infusion rate by 50%. Closely monitor for worsening signs or symptoms. Medical management as needed. Subsequent infusions should be given after appropriate premedication and at the reduced infusion rate.
Grade 2 - Moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, corticosteroids, and/or intravenous fluids); prophylactic medications indicated for ≤ 24 hours.	Stop infusion. Infusion may be resumed at 50% of previous rate once infusion-related reaction has resolved or decreased to Grade 1 in severity. Closely monitor for worsening signs or symptoms. Appropriate 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 observation or clinical management.	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.

Abbreviation: NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

If the infusion rate of study drug(s) has been decreased by 50% or suspended due to an infusion-related reaction, this decreased rate must be maintained for all subsequent infusions and be administered 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.

For the prophylaxis of mild events (eg, nasal congestion or flu-like symptoms), a dose of 25 mg indomethacin or a comparable dose of nonsteroidal anti-inflammatory drugs (eg, 600 mg ibuprofen or 500 mg naproxen sodium) may be administered 2 hours before and 8 hours after the start of each dose of study drugs(s) infusion. Alternative treatments for fever (eg, paracetamol) may be given to patients at the discretion of the investigator.

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grade 1 or 2 Infusion Reaction: Proper medical management should be instituted as indicated per the type of reaction. This includes, but is not limited to, an antihistamine (eg, diphenhydramine), an antipyretic (eg, paracetamol), and if considered indicated, oral or intravenous glucocorticoids, epinephrine, bronchodilators, and oxygen. In subsequent cycles, the patient should receive oral premedication with an antihistamine (eg, diphenhydramine) and an antipyretic (eg, paracetamol), and should be closely monitored for clinical signs and symptoms of an infusion reaction.

NCI-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 intravenous antihistamines, antipyretics, glucocorticoids, epinephrine, bronchodilators, and oxygen.

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

The patient will be administered epinephrine injection and dexamethasone infusion if severe hypersensitivity reaction is observed. The patient should be closely monitored, and intensive care unit should be alerted for possible transfer as indicated.

Evaluation of Immune-Mediated Adverse Events

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

The recommendations for diagnostic evaluation and management of immune-mediated adverse events are based on European Society for Medical Oncology and American Society of Clinical Oncology guidelines (Haanen et al 2017, Brahmer et al 2018). For any adverse events not included in the tables below, refer to the American Society of Clinical Oncology Clinical

Practice Guideline (Brahmer et al 2018) for further guidance on diagnostic evaluation and management of immune-mediated toxicities.

Criteria used to diagnose immune-mediated adverse events 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 immune-mediated adverse event diagnosis:

- What was the temporal relationship between initiation of tislelizumab and the adverse event?
- How did the patient respond to withdrawal 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 immune-mediated adverse event field associated with the adverse event in the electronic case report form should be checked. If further diagnostic evaluations change the assessment, the electronic case report form should be updated accordingly.

Recommended Diagnostic Tests in the Management of Possible Immune-Mediated Adverse Events

Immune-Mediated 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

Recommended Diagnostic Tests in the Management of Possible Immune-Mediated Adverse Events

Immune-Mediated Toxicity	Diagnostic Evaluation Guideline
	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 Grades 3 and 4; every 2 to 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.
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, CK/CK-MB, troponin (I and/or T), and refer to a cardiologist.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; CK, creatine kinase; CK-MB, creatine kinase cardiac isoenzyme; CNS, central nervous system; CRP, C-reactive protein; CT, computed tomography; DLCO, carbon monoxide diffusion capacity; ESR, erythrocyte sedimentation rate; FBC, full blood count; INR, international normalized ratio; LCI, liver cytosolic antigen; LFT, liver function test; LKM, liver kidney microsomal antibody; LP, liver pancreas antigen; MRA, magnetic resonance angiogram; SLA, soluble liver antigen; SMA, smooth muscle antibody; T4, thyroxine; TFT, thyroid function test; TSH, thyroid-stimulating hormone; UEC, urea, electrolytes, and creatinine.

Management of Immune-Mediated Adverse Events

Immune-mediated adverse events can escalate quickly. Study treatment interruption, close monitoring, timely diagnostic work-up, and treatment intervention as appropriate is required. Immune-mediated adverse events 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.

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 after restart of study drug should permanently discontinue treatment.

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. For France only: Tislelizumab must be permanently discontinued for any onset of Grade 4 or recurrent Grade 3 immune-mediated adverse events.

Steroid dosages in the table below are for oral or intravenous (methyl)prednisolone. Equivalent dosages of other corticosteroids can be substituted. For steroid-refractory immune-mediated adverse events, consider use of steroid-sparing agents (eg, mycophenolate mofetil). Consider prophylactic antibiotics for opportunistic infections if the patient is receiving long-term immunosuppressive therapy.

Management of Immune-Mediated Adverse Events

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	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 to 4 weeks. Monitor thyroid function regarding the need for hormone replacement.	Continue study treatment or withhold treatment in cases with systemic symptoms.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Study Drug Management
	3-4 Severe symptoms, hospitalization required	Refer patient to an endocrinologist. If hypothyroid, replace with thyroxine 0.5 to 1.6 µg/kg/day (for the elderly or those with co-morbidities, 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.	Hold study treatment; resume when resolved/improved to Grades 0 and 1. For France only: For Grade 3: Hold study treatment; resume when resolved/improved to Grades 0 and 1. For recurrent Grade 3: Discontinue study treatment. For Grade 4: Discontinue study treatment
Hypophysitis	**1-2** Mild to moderate symptoms	Refer patient to an endocrinologist for hormone replacement. Add oral prednisolone 0.5 to 1 mg/kg/day for patients with pituitary inflammation. Taper corticosteroids over ≥ 1 month. If there is no improvement in 48 hours, treat as Grades 3 and 4. Taper corticosteroids over ≥ 1 month.	Continue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Study Drug Management
	3-4 Severe or life-threatening 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 ≥ 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. For France only: For Grade 3: Hold study treatment; resume when resolved/improved to Grades 0 and 1. Discontinuation is usually not necessary. For recurrent Grade 3: Discontinue study treatment. For Grade 4: Discontinue study treatment
Pneumonitis	**1** Radiographic changes only	Monitor symptoms every 2 to 3 days. If appearance worsens, treat as Grade 2.	Consider holding study treatment until appearance improves and cause is determined.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Study Drug Management
	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 ≥ 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.
	3-4 Severe or life-threatening symptoms Breathless at rest	Admit to a hospital and initiate treatment with IV methylprednisolone 2 to 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 ≥ 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 to 1 mg/kg/day. Taper over ≥ 4 weeks. Obtain neurology consultation.	Hold study treatment; resume when resolved/improved to Grades 0 and 1.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Study Drug Management
	3-4 Severe/life-threatening	Initiate treatment with oral prednisolone or IV methylprednisolone 1 to 2 mg/kg/day, depending on symptoms. Taper corticosteroids over ≥ 4 weeks. Consider azathioprine, MMF, cyclosporine if no response within 72 to 96 hours.	Discontinue study treatment.
Colitis/Diarrhea	**1** Mild symptoms: < 4 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 to 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 to 4 weeks, consider endoscopy if symptoms are recurring.	Hold study treatment; resume when resolved/improved to baseline grade.
	3 Severe symptoms: > 7 liquid stools per day over baseline, or if episodic within 1 hour of eating	Initiate IV methylprednisolone 1 to 2 mg/kg/day. Convert to oral prednisolone and taper over ≥ 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,	Hold study treatment; retreatment may be considered when resolved/improved to baseline grade and after discussion with the study medical monitor. For France only: For recurrent Grade 3: Discontinue study treatment

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Study Drug Management
	4 Life-threatening symptoms	hepatitis, NYHA grade III/IV CHF or other immunosuppressive treatment: MMF or tacrolimus. Consult gastroenterologist to conduct colonoscopy/ sigmoidoscopy.	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% to 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 judgment: For moderate symptoms: oral prednisolone 0.5 to 1 mg/kg/day for 3 days then taper over 2 to 4 weeks. For severe symptoms: IV methylprednisolone 0.5 to 1 mg/kg/day; convert to oral prednisolone and taper over ≥ 4 weeks.	Hold study treatment. Re-treat when AE is resolved or improved to mild rash (Grades 1 and 2) after discussion with the study medical monitor. For France only: For recurrent Grade 3: Discontinue study treatment

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Study Drug Management
	4 Skin sloughing > 30% BSA with associated symptoms (eg, erythema, purpura, epidermal detachment), <<Add text for France only: including Stevens-Johnson syndrome (all grade), and toxic epidermal necrolysis>>	Initiate IV methylprednisolone 1 to 2 mg/kg/day. Convert to oral prednisolone and taper over ≥ 4 weeks. Admit to a hospital and seek urgent dermatology consultation.	Discontinue study treatment.
Hepatitis	**1** ALT or AST > ULN to 3 x 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 to 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 to 5 x ULN	Recheck LFTs every 48 to 72 hours: For persistent ALT/AST elevation: consider oral prednisolone 0.5 to 1 mg/kg/day for 3 days then taper over 2 to 4 weeks. For rising ALT/AST: start oral prednisolone 1 mg/kg/day and taper over 2 to 4 weeks; re-escalate dose if LFTs worsen, depending on clinical judgment.	Hold study treatment; treatment may be resumed when resolved/improved to baseline Grade and prednisolone tapered to ≤ 10 mg.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Study Drug Management
	3 ALT or AST 5 x to 20 x ULN Guidance to authors: Note that ASCO/ESMO guidance is to discontinue for Grade 3. Labels for other PD-(L)1 inhibitors recommend treatment discontinuation for ALT or AST levels as follows: Atezolizumab: > 8 x ULN Nivolumab: > 8 x ULN Pembrolizumab: > 8 x ULN	ALT/AST < 400 IU/L and normal bilirubin/INR/albumin: Initiate oral prednisolone 1 mg/kg and taper over ≥ 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 ≥ 4 weeks.	If ALT and AST ≤ 10 x ULN: Hold study treatment until improved to baseline Grade; reintroduce only after discussion with the study medical monitor. If ALT or AST > 10 x ULN: Discontinue study treatment. For France only: If ALT or AST ≤ 8 x ULN or total bilirubin ≤ 5 x ULN: Hold study treatment until improved to baseline grade; reintroduce only after discussion with the study medical monitor For France only: If ALT or AST > 8 x ULN or total bilirubin > 5 x ULN: Discontinue study treatment. For France only: For recurrent Grade 3: Discontinue study treatment.
	4 ALT or AST > 20 x ULN	Initiate IV methylprednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over ≥ 6 weeks.	Discontinue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Study Drug Management
	Worsening LFTs despite steroids: If on oral prednisolone, change to pulsed IV methylprednisolone If on IV methylprednisolone, add MMF 500 to 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 1.5 x baseline or > ULN to 1.5 x ULN	Repeat creatinine weekly. If symptoms worsen, manage as per criteria below.	Continue study treatment.
	2 Creatinine > 1.5 x to 3 x baseline or > 1.5 x to 3 x ULN	Ensure hydration and review creatinine in 48 to 72 hours; if not improving, consider creatinine clearance measurement by 24-hour urine collection. Discuss with nephrologist the need for kidney biopsy. If attributed to study drug, initiate oral prednisolone 0.5 to 1 mg/kg and taper over ≥ 2 weeks. Repeat creatinine/U&E every 48 to 72 hours.	Hold study treatment. If not attributed to drug toxicity, restart treatment. If attributed to study drug and resolved/improved to baseline grade: Restart study drug if tapered to < 10 mg prednisolone.
	3 Creatinine > 3 x baseline or > 3 x to 6 x 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 to 2 mg/kg. Taper corticosteroids over ≥ 4 weeks.	Hold study treatment until the cause is investigated. If study drug suspected: Discontinue study treatment. <<Add text for France only: For recurrent Grade 3: Discontinue study treatment.>>
	4 Creatinine > 6 x ULN	As per Grade 3, patient should be managed in a hospital where renal replacement therapy is available.	Discontinue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Study Drug Management
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 to 250 mg/dL; 8.9 to 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 Grades 0 and 1.
	3 Fasting glucose value 250 to 500 mg/dL; 13.9 to 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 Grades 0 and 1. For France only: For recurrent Grade 3: Discontinue study treatment
	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.	Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grades 0 and 1. For France only: (split Grade 3 and 4): Discontinue study treatment

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Study Drug Management
Ocular Toxicity	**1** Asymptomatic eye examination/test abnormality	Consider alternative causes and prescribe topical treatment as required.	Continue study treatment.
	2 Anterior uveitis or mild symptoms	Refer patient to an ophthalmologist for assessment and topical corticosteroid treatment. Consider a course of oral steroids.	Continue study treatment or hold treatment if symptoms 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 to 2 mg/kg and taper over ≥ 4 weeks.	Hold study treatment until improved to Grades 0 and 1; reintroduce only after discussion with the study medical monitor. For France only: For recurrent Grade 3: Discontinue study treatment
	4 Blindness (≥ 20/200) in the affected eyes	Initiate IV (methyl)prednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over ≥ 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 to 2 mg/kg/day. Convert to oral prednisolone when amylase/lipase improved to Grade 2, and taper over ≥ 4 weeks.	Hold study treatment; reintroduce only after discussion with the study medical monitor. For France only: For recurrent Grade 3: Discontinue study treatment

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Study Drug Management
	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 Grades 0 and 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 to 1 mg/kg and taper over ≥ 4 weeks.	Hold study treatment unless improved to Grades 0 and 1; reintroduce only after discussion with the study medical monitor. For France only: For recurrent Grade 3: Discontinue study treatment
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 oral intake, limited instrumental activities	As per local guidelines, treat with analgesics, topical treatments and oral hygiene care. Ensure adequate hydration. If symptoms worsen or there is sepsis or bleeding, manage as a Grade 3 event.	Continue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Study Drug Management
	3 Severe pain, limited food and fluid intake, daily living activity limited	Admit to hospital for appropriate management. Initiate IV (methyl)prednisolone 1 to 2 mg/kg/day. Convert to oral prednisolone when symptoms improved to Grade 2 and taper over ≥ 4 weeks.	Hold study treatment until improved to Grades 0 and 1. For France only: For recurrent Grade 3: Discontinue study treatment
	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 to 1 mg/kg and taper over ≥ 4 weeks	Hold study treatment until improved to Grades 0 and 1.
	3-4 Severe weakness, limiting self-care	Admit to hospital and initiate oral prednisolone 1 mg/kg. Consider bolus IV (methyl)prednisolone and 1 to 2 mg/kg/day maintenance for severe activity restriction or dysphagia. If symptoms do not improve add immunosuppressant therapy. Taper oral steroids over ≥ 4 weeks	For Grade 3: Hold study treatment until improved to Grades 0 and 1. Discontinue if any evidence of myocardial involvement. For France only: For recurrent Grade 3: Discontinue study treatment. For Grade 4: Discontinue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Study Drug Management
Myocarditis[a]	**< 2** Asymptomatic but significantly increased CK-MB or increased troponin OR clinically significant intraventricular conduction delay	Initiate cardiac evaluation under close monitoring with repeat serum testing and ECG, cardiac echo/MUGA, and /or other interventions per institiutional guidelines; consider referral to a cardiologist. If diagnosis of myocarditis is confirmed, treat as Grade 2	Hold study treatment. If a diagnosis of myocarditis is confirmed, permanently discontinue study treatment in patients with moderate or severe symptoms. Patients with no symptoms or mild symptoms may not restart tislelizumab unless cardiac parameters have returned to baseline and after discussion with the study medical monitor.
	2 Symptoms on mild-moderate exertion	Admit to hospital and initiate oral prednisolone or IV (methyl)prednisolone at 1 to 2 mg/kg/day. Consult with a cardiologist and 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	
	3 Severe symptoms with mild exertion		

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Study Drug Management
	4 Life-threatening		Hold study treatment. If a diagnosis of myocarditis is confirmed and considered immune related, permanently discontinue study treatment in patients with moderate or severe symptoms. Patients with no symptoms or mild symptoms may not restart tislelizumab unless cardiac parameters have returned to baseline and after discussion with the study medical monitor. For France only: Discontinue study treatment

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; ASCO, American Society of Clinical Oncology; AST, aspartate aminotransferase; BSA, body surface area; CHF, congestive heart failure; CK, creatine kinase; CK-MB, creatine kinase cardiac isoenzyme; ESMO, European Society for Medical Oncology; INR, international normalized ratio; IV, intravenous; LFT, liver function test; MMF, mycophenolate mofetil; MUGA, multigated acquisition; NYHA, New York Heart Association; PD-(L)1, programmed death (ligand)-1; T4, thyroxine; TB, tuberculosis; TFT, thyroid function test; TSH, thyroid-stimulating hormone; U&E, urea and electrolytes; ULN, upper limit of normal.

[a] If clinically significant cardiac enzyme abnormalities are detected during laboratory assessment and serial cardiac enzyme assessments pose logistical hardship for the patient, then patient hospitalization should strongly be considered until immune-mediated myocarditis has been ruled out.

APPENDIX 10. CYP3A INHIBITORS AND INDUCERS

Strong CYP3A Inhibitors
Antibiotics: clarithromycin, telithromycin, troleandomycin
Antifungals: itraconazole, ketoconazole, posaconazole, voriconazole
Antivirals: boceprevir, telaprevir
Food products: grapefruit juice [a]
Other: cobicistat, conivaptan, elvitegravir, nefazodone, diltiazem, idelalisib
Protease inhibitors: nelfinavir, ritonavir or ritonavir [b] in combination with danoprevir/elvitegravir/indinavir/lopinavir/paitprevir and (obitasvir and/or dasabuvir)/saquinavir/tipranavir
Moderate CYP3A Inhibitors
Antibiotics: ciprofloxacin, erythromycin
Antifungals: fluconazole, clotrimazole
Calcium channel blockers: verapamil
Tyrosine kinase inhibitors (anticancer): imatinib, crizotinib
Others: aprepitant, cimetidine, cyclosporine, dronedarone, tofisopam, fluvoxamine
Strong CYP3A Inducers
Carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort
Moderate CYP3A Inducers
Bosentan, efavirenz, etravirine, modafinil

Source: Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers (9/26/2016).
Abbreviations: CYP3A, cytochrome P450, family 3, subfamily A; HCV, hepatitis C virus.
Note: The list of drugs in this table is not exhaustive. Please refer to the prescribing information of concomitant medication to check for CYP3A inhibition or induction risks or contact the medical monitor of the protocol.

[a.] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (eg, low dose, single strength).

[b.] Ritonavir is usually given in combination with other anti-HIV or anti-HCV drugs in clinical practice. Caution should be used when extrapolating the observed effect of ritonavir alone to the effect of combination regimens on CYP3A activities.

APPENDIX 11. DOSE MODIFICATION TABLE FOR ZANUBRUTINIB WHEN COADMINISTERED WITH STRONG/MODERATE CYP3A INHIBITORS OR INDUCERS

CYP3A	Coadministered 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

Source: Food and Drug Administration Center for Drug Evaluation Research. FDA Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing and Labeling Recommendations. 2012.
Abbreviations: CYP3A, cytochrome P450, family 3, subfamily A; FDA, Food and Drug Administration .
Note: The list of drugs in this table is not exhaustive. Please refer to the prescribing information of concomitant medication to check for CYP3A inhibition or induction risks or contact the medical monitor of the protocol.

APPENDIX 12. CHRONIC KIDNEY DISEASE EPIDEMIOLOGY COLLABORATION (CKD-EPI) EQUATION

In adults, the most widely used equations for estimating glomerular filtration rate (GFR) from serum creatinine are the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey et al 2009) and the Modification of Diet in Renal Disease Study equation. The National Kidney Disease Education Program calculators rely on creatinine determinations which are isotope dilution mass spectrometry traceable. All laboratories should be using creatinine methods calibrated to be isotope dilution mass spectrometry traceable.

This CKD-EPI equation calculator should be used when Scr reported in mg/dL. This equation is recommended when eGFR values above 60 mL/min/1.73 m^2 are desired.

$GFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times 1.159$ [if Black]

where:

S_{cr} is serum creatinine in mg/dL,

κ is 0.7 for females and 0.9 for males,

α is -0.329 for females and -0.411 for males,

min indicates the minimum of S_{cr}/κ or 1, and

max indicates the maximum of S_{cr}/κ or 1.

The equation does not require weight because the results are reported normalized to 1.73 m^2 body surface area, which is an accepted average adult surface area.

The online calculator for CKD-EPI can be found here: https://www.niddk.nih.gov/health-information/communication-programs/nkdep/laboratory-evaluation/glomerular-filtration-rate-calculators.

APPENDIX 13. THE LUGANO CLASSIFICATION FOR NON-HODGKIN LYMPHOMA (CHESON 2014)

Response and Site	PET-CT-Based Response	CT-Based Response
Complete Response	Complete metabolic response	Complete radiologic response (all of the following):
Lymph nodes and extra-lymphatic sites	Score 1, 2, 3[a] with or without a residual mass on 5PS[b] It is recognized that in Waldeyer's ring or extra-nodal sites with physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic 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 extra-lymphatic sites of disease
Non-measured lesions	Not applicable	Absent
Organ enlargement[c]	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology (if BMA involved at screening) If indeterminate, IHC negative
Partial Response	Partial metabolic response:	Partial remission (all of the following):
Lymph nodes and extra-lymphatic 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 extra-nodal 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
Non-measured lesions	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

Response and Site	PET-CT-Based Response	CT-Based Response
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, extra-nodal lesions	Score 4 or 5[b] 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 extra-nodal sites; no criteria for progressive disease are met
Non-measured lesions	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 disease	Progressive disease requires ≥ 1 of the following:
Individual target nodes/nodal masses	Score 4 or 5[b] 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	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 o 0.5 cm for lesions ≤ 2 cm o 1.0 cm for lesions > 2 cm
Non-measured lesions	None	New lesions or clear progression of pre-existing non-measured lesions: • 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

Response and Site	PET-CT-Based Response	CT-Based Response
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	
Organ enlargement	Not applicable	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 no prior splenomegaly, must increase by ≥ 2 cm from baseline
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, [^{18}F] fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion;; PET, positron emission tomography

Note: Modified from Cheson BD, Fisher RJ, Barrington SF, et al. J Clin Oncol 2014;32(27):3059-68.

[a] A score 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in studies 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 6 of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in 2 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), gastrointestinal involvement, cutaneous lesions, or those noted on palpation. Non-measured 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, gastrointestinal tract, liver, bone marrow), FDG uptake may be greater than in 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 5PS (Deauville Criteria):

1. No uptake above background
2. Uptake ≤ mediastinum
3. Uptake > mediastinum but ≤ liver
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

Note: Temporary withholding of study drug (eg, for drug-related toxicity, surgery, or intercurrent illness) for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. In such circumstances, and if medically appropriate, patients may resume therapy and relevant clinical, laboratory, and/or radiologic assessments should be performed to document whether tumor control can be maintained or whether actual disease progression has occurred.

[c] Isolated increase in lymph nodes and/or splenomegaly during periods of zanubrutinib hold will not be considered as disease progression unless confirmed by a repeat imaging study ≥ 6 weeks after restarting study drug administration. The response category "indeterminate due to zanubrutinib hold" should be selected for such instances. Following the repeat imaging 6 weeks after restarting study drug, response should be in comparison to the imaging at baseline

APPENDIX 14. CLL RESPONSE DEFINITIONS (IWCLL 2018)

Parameter	CR[a]	PR	PR-L	PD	Stable Disease
Group A					
Lymph Nodes	None ≥ 1.5 cm	Decrease ≥ 50% (from baseline)[b]	Decrease ≥ 50% from baseline	Increase ≥ 50% from baseline or from response	Change of − 49% to + 49%
Liver and/or Spleen Size[c]	Spleen size < 13 cm; liver size normal	Decrease ≥ 50% (from baseline)	Decrease ≥ 50% from baseline	Increase ≥ 50% from baseline or from response	Change of − 49% to + 49%
Constitutional Symptoms	None	Any	Any	Any	Any
Circulating Lymphocyte Count	Normal	Decrease ≥ 50% from baseline	Decrease < 50% or increase from baseline	Increase ≥ 50% from baseline[d]	Change of − 49% to + 49%
Group B					
Platelet Count	≥ 100 x 10^9/L	≥ 100 x 10^9/L or increase ≥ 50% over baseline	> 100,000/μL or increase ≥ 50% over baseline	Decrease of ≥ 50% from baseline secondary to CLL	Change of − 49% to + 49%
Hemoglobin	≥ 11.0 g/dL (untransfused and without erythropoietin)	≥ 11 g/dL or increase ≥ 50% over baseline	> 11 g/dL or increase ≥ 50% over baseline	Decrease of ≥ 2 g/dL from baseline secondary to CLL	Increase < 11.0 g/dL or < 50% over baseline, or decrease < 2 g/dL
Bone Marrow Biopsy	Normocellular, no CLL cells, no B-lymphoid nodules	Presence of CLL cells, or of B-lymphoid nodules, or not done	Presence of CLL cells, or of B-lymphoid nodules, or not done	Increase of CLL cells by ≥ 50% on successive biopsies	No change in marrow infiltrate

Source: Hallek et al 2018; Cheson et al 2012

Abbreviations: CLL, chronic lymphocytic leukemia; CR, complete remission (response); CRi, CR with incomplete bone marrow recovery; CT, computed tomography; PD, disease progression; PR, partial remission (response); PR-L, partial remission (response) with lymphocytosis

Note: Parameters of Group A assess the lymphoid tumor load and constitutional symptoms; parameters of Group B assess the hematopoietic system.

CR: all of the criteria have to be met; PR: ≥ 2 of the parameters of Group A and 1 parameter of Group B need to improve if previously abnormal; if only 1 parameter of both Groups A and B is abnormal before therapy, only 1 of either Group A or Group B needs to improve; PR-L: presence of lymphocytosis, plus ≥ 50% reduction in lymphadenopathy and/or in spleen or liver enlargement, plus one of the criteria for platelets, hemoglobin, or bone marrow biopsy have to be met; PD: ≥ 1 of the criteria of Group A or Group B has to be met; SD: all of the criteria have to be met, constitutional symptoms alone do not define PD.

[a] Some patients fulfill all the criteria for a CR, but have a persistent anemia, thrombocytopenia, or neutropenia apparently unrelated to CLL, but related to drug toxicity. These patients should be considered as a different category of remission, CR with incomplete marrow recovery (CRi). For the definition of this category, the marrow evaluation should be performed with scrutiny and not show any clonal disease infiltrate.

[b] Sum of the products of 6 or fewer lymph nodes (as evaluated by CT scans and by physical examination).

[c] Spleen size is considered normal if < 13 cm.

[d] In the absence of other objective evidence of PD, lymphocytosis alone should not be considered an indicator of PD (Cheson et al 2012).

Temporary withholding of study drug (eg, for drug-related toxicity, surgery, or intercurrent illness) for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. In such circumstances, and if medically appropriate, patients may resume therapy and relevant clinical, laboratory, and/or radiologic assessments should be performed to document whether tumor control can be maintained or whether actual disease progression has occurred.

Isolated increase in lymph nodes and/or splenomegaly (defined as vertical spleen length > 13 cm) during periods of zanubrutinib hold will not be considered as disease progression unless confirmed by a repeat imaging study ≥ 6 weeks after restarting study drug administration. The response category “indeterminate due to zanubrutinib hold” should be selected for such instances. Following the repeat imaging 6 weeks after restarting study drug, response should be in comparison to the imaging at baseline.

APPENDIX 15. GRADING SCALE FOR HEMATOLOGIC TOXICITY IN CLL STUDIES

Grade[a]	Decrease in Platelets[b] or Hgb[c] (Nadir) From Pretreatment Value	Absolute Neutrophil Count (Nadir) x 10^9/L[d]
0	No change to 10%	≥ 2
1	11% to 24%	≥ 1.5 and < 2
2	25% to 49%	≥ 1 and < 1.5
3	50% to 74%	≥ 0.5 and < 1
4	≥ 75%	< 0.5

Source: Hallek et al 2018.

Abbreviation: ANC, absolute neutrophil count; CLL, chronic lymphocytic leukemia; Hgb, hemoglobin; WBC, white blood cell.

a. Grades: 1, mild; 2, moderate; 3, severe; 4, life-threatening; 5, fatal. Death occurring as a result of toxicity at any level of decrease from pretreatment will be reported as Grade 5.

b. Platelet counts must be below normal levels for Grades 1 to 4. If, at any level of decrease, the platelet count is < 20 x 10^9/L, this will be considered Grade 4 toxicity, unless a severe or life-threatening decrease in the initial platelet count (eg, < 20 x 10^9/L) was present pretreatment, in which case the patient is not evaluable for toxicity referable to platelet counts.

c. Hgb levels must be below normal levels for Grades 1 to 4. Baseline and subsequent Hgb determinations must be performed before any given transfusions. The use of erythropoietin is irrelevant for the grading of toxicity, but should be documented.

d. If the ANC reaches < 1 x 10^9/L, it should be judged to be Grade 3 toxicity. Other decreases in the WBC, or in circulating granuloctyes are not to be considered because a decrease in the WBC is a desired therapeutic endpoint. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. If the ANC was < 1 x 10^9/L before therapy, the patient is not evaluable for toxicity referable to the ANC. The use of growth factors such as granulocyte colony-stimulating factor is not relevant to the grading of toxicity but should be documented.

APPENDIX 16. ECOG PERFORMANCE STATUS

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

As published by (Oken et al 1982). Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

APPENDIX 17. THE RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) GUIDELINES, VERSION 1.1

The text below was obtained from the following reference:

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228 47.

Definitions

Response and progression will be evaluated in this trial using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (v1.1). Changes in only the largest diameter (uni-dimensional measurement) of the tumor lesions are used in the RECIST criteria.

Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

Measurable Disease

Tumor lesions: Must be accurately measured in ≥ 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT and MRI (no less than double the slice thickness and a minimum of 10 mm). Assumes a scan slice thickness no greater than 5 mm.
- 10 mm caliper measurement by clinical exam (when superficial)
- 20 mm by chest X-ray (if clearly defined and surrounded by aerated lung)

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Nonmeasurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered nonmeasurable disease. Leptomeningeal disease, ascites, pleural, or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques are all non-measurable.

Bone lesions:

- Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above
- Blastic bone lesions are nonmeasurable

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Trial protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan, this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but < 15 mm) should be considered nontarget lesions. Nodes that have a short axis < 10 mm are considered nonpathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Nontarget Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present", "absent", or in rare cases "unequivocal progression" (more details to follow). In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (eg, "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

Guidelines For Evaluation Of Measurable Disease

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

- Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the trial.
- Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scans).

- Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.
- Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.
- Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in CR. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and prostate-specific antigen response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.
- Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

Response Criteria

Evaluation of Target Lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of ≥ 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study
- Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report form may be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.
- Target lesions that become "too small to measure". While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure".
  When this occurs, it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.
- Lesions that split or coalesce on treatment: When non-nodal lesions "fragment", the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion".

Evaluation of Nontarget Lesions

While some nontarget lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- CR: Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (<10 mm short axis).
- Non-CR/Non-PD: Persistence of one or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits
- PD: Unequivocal progression (as detailed below) of existing nontarget lesions. (Note: the appearance of one or more new lesions is also considered progression.)
- When the patient also has measurable disease: In this setting, to achieve "unequivocal progression" on the basis of the nontarget disease, there must be an overall level of substantial worsening in nontarget disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more nontarget lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in nontarget disease in the face of SD or PR of target disease will therefore be extremely rare.
- When the patient has only non-measurable disease: This circumstance arises in some phase 3 trials when it is not a criterion of trial entry to have measurable disease. The same general concept applies here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase diameter in a measurable lesion).
- Examples include an increase in a pleural effusion from "trace" to "large", an increase in lymphangitic disease from localized to widespread, or may be described in protocols as "sufficient to require a change in therapy". If "unequivocal progression" is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example,

necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified on a follow-up trial in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on trial has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While fluorodeoxyglucose (FDG)-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible "new" disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up, is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- Timepoint Response
    - It is assumed that at each protocol specified time point, a response assessment occurs. The following table provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline:

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD

Target Lesions	Non-target Lesions	New Lesions	Overall Response
Any	Any	Yes	PD

Abbreviations: CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

When patients have non-measurable (therefore non-target) disease only, the following table is to be used:

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	SD (Non-CR/non-PD)
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Evaluation of Best Overall Response

The BOR is the best response recorded from the start of the study drug treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of BOR. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's BOR assignment will depend on the findings of both target and nontarget disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the trial and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "best overall response".

The BOR is determined once all the data for the patient is known.

Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a BOR of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later).

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero."

In trials where confirmation of response is required, repeated "NE" time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping trial therapy.

Conditions that define "early progression, early death, and inevaluability" are trial specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of CR. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/ sensitivity.

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes, or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

Confirmation

In nonrandomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, ie, in randomized trials (phase 2 or 3) or trials where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in trials which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after trial entry at a minimum interval (in general not less than 6 weeks).

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between 2 measurements for determination of stable disease.

Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity, and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

APPENDIX 18. PRE-EXISTING IMMUNE DEFICIENCIES OR AUTOIMMUNE DISEASES

Prospective patients should be carefully questioned to determine whether they have any history of an acquired or congenital immune deficiency or autoimmune disease.

Please contact the sponsor medical monitor regarding any uncertainty about immune deficiency/autoimmune disease exclusions.

Acute disseminated encephalomyelitis	Addison's disease
Ankylosing spondylitis	Antiphospholipid antibody syndrome
Aplastic anemia	Autoimmune hemolytic anemia
Autoimmune hepatitis	Autoimmune hypoparathyroidism
Autoimmune hypophysitis	Autoimmune myocarditis
Autoimmune oophoritis	Autoimmune orchitis
Autoimmune thrombocytopenic purpura	Behcet's disease
Bullous pemphigoid	Chronic inflammatory demyelinating polyneuropathy
Chung-Strauss syndrome	Crohn's disease
Dermatomyositis	Dysautonomia
Epidermolysis bullosa acquisita	Gestational pemphigoid
Giant cell arteritis	Goodpasture's syndrome
Granulomatosis with polyangiitis	Graves' disease
Guillain-Barré syndrome	Hashimoto's disease
Immunoglobulin A neuropathy	Inflammatory bowel disease
Interstitial cystitis	Kawasaki's disease
Lambert-Eaton myasthenia syndrome	Lupus erythematosus
Lyme disease (chronic)	Mooren's ulcer
Morphea	Multiple sclerosis
Myasthenia gravis	Neuromyotonia
Opsoclonus myoclonus syndrome	Optic neuritis
Ord's thyroiditis	Pemphigus
Pernicious anemia	Polyarteritis nodusa
Polyarthritis	Polyglandular autoimmune syndrome
Primary biliary cirrhosis	Psoriasis
Reiter's syndrome	Rheumatoid arthritis
Sarcoidosis	Sjögren's syndrome

Stiff person syndrome	Takayasu's arteritis
Ulcerative colitis	Vogt-Kovangai-Harada disease

APPENDIX 19. SIGNATURE OF INVESTIGATOR

PROTOCOL TITLE: A Phase 1/2, Dose Escalation and Expansion Study of BGB-10188, a Phosphatidylinositol 3-Kinase Delta (PI3Kδ) Inhibitor, Combined With Zanubrutinib in Patients With Mature B-Cell Malignancies and Combined With Tislelizumab in Patients With Solid Tumors

PROTOCOL NO: BGB-A317-3111-10188-101

This protocol is a confidential communication of BeiGene, Ltd., and its affiliates. I confirm that I have read this protocol, I understand it, and I will work according to this protocol and the terms of the clinical study agreement governing the study. 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, Ltd., or one of its affiliates.

Instructions to the Investigator: Please SIGN and DATE this signature page prior to implementation of this sponsor-approved protocol. PRINT your name, title, and the name and address of the center in which the study will be conducted.

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 20. EVALUATION OF RESPONSE ACCORDING TO CA-125

The text below was obtained from the following reference (Gordon John Sampson Rustin):

Definitions for Response and Progression in Ovarian Cancer Clinical Trials Incorporating RECIST 1.1 and CA-125 Agreed by the Gynecological Cancer Intergroup (GCIG). Int J Gynecol Cancer. 2011;21:419-23.

Definition of Response:

A carcinoma antigen-125 (CA-125) response is defined as at least a 50% reduction in CA-125 levels from a pretreatment sample. The response must be confirmed and maintained by using the next scheduled CA-125 data (at least 28 days). Patients can be evaluated according to CA-125 only if they have a pretreatment sample that is at least twice the upper limit of the reference range and within 2 weeks before starting the treatment.

To calculate CA-125 responses accurately, the following rules apply:

- Intervening samples and the 28-day confirmatory sample must be less than or equal to (within an assay variability of 10%) the previous sample.
- Variations within the reference range of CA-125 levels will not interfere with the response definition.
- For each patient, the same assay method must be used, and the assay must be tested in a quality control scheme.
- Patients are not evaluable by CA-125 if they have received mouse antibodies (unless the assay used has been shown not to be influenced by human anti-mouse antibody) or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days (eg, paracentesis). If assessing a therapy that includes 2 treatment modalities for relapse (eg, surgery and chemotherapy), any CA-125 response could be a result from either or both treatment modalities. In this case, CA-125 cannot distinguish between the effects of the 2 treatments.

The date when the CA-125 level is first reduced by 50% is the date of the CA-125 response.

To calculate response, an intent-to-treat analysis should be used that includes all patients with an initial CA-125 level of at least twice the upper limit of the reference range as eligible and evaluable. In addition, as a separate analysis, those patients who have a CA-125 response and whose CA-125 level falls to within the reference range can be classified as CA-125 complete responder. Patients who have a fall of CA-125 to within the reference range but whose initial CA-125 was less than twice the upper limit of the reference range cannot therefore be classified as a CA-125 complete responder.

CA-125 Response Measurement

CA-125 Level	CA-125 Measurement
Baseline CA-125 more than twice the upper limit of normal, later reduced by 50% to normal and maintaining for at least 28 days	CR
Baseline CA-125 more than twice the upper limit of normal, later reduced by 50% but not to normal	PR
CA-125 change out of range of PR and PD	Non-PR, non-PD
CA-125 increased at baseline returning to normal after treatment, later twice or higher than the upper limit of normal (2 consecutive measurements at an interval of at least 1 week)	Progressive disease (date of first evaluation of progression)
CA-125 increased at baseline not returning to normal after treatment, later twice or higher than the lowest value (2 consecutive measurements at an interval of at least 1 week)	Progressive disease (date of first evaluation of progression)
CA-125 within the reference range at baseline, later twice or higher than the upper limit of normal (2 consecutive measurements at an interval of at least 1 week)	Progressive disease (date of first evaluation of progression)

Abbreviations: CA-125, carcinoma antigen-125; CR, complete response; PR, partial response

Evaluation of Best Overall Response in Patients With Measurable Disease and Who Are Also Evaluable by CA-125

Target Lesion*	Nontarget†	New Lesion	CA-125	Overall Best Response
CR	CR	No	Normal	CR
CR	Non-CR or non-PD	No	Not PD	PR
CR	CR	No	PR but not normal	PR
CR	NE	No	PR	PR
PR	Non-PD or NAE	No	Not PD	PR
NAE	Non-PD	No	PR	PR
PD or New > 28 days from CA-125 PR‡			PR	PR
Stable disease§	Non-PD	No	PR	PR
Stable disease§	Non-PD or NAE	No	Not PR and not PD	Stable disease
PD or New ≤ 28 days from CA-125 PR‡			PR	PD
PD	Any	Yes or no	Any	PD
Any	PD	Yes or no	Any	PD
Any	Any	Yes	Any	PD
Any	Any	Yes or no	PD	PD

Abbreviations: CA-125, carcinoma antigen-125; CR, complete response; NE, not evaluated; NAE, not all evaluated; PR, partial response.

*Target lesions include up to 5 measurable lesions (2 per organ) as defined by RECIST v1.1.

†Nontarget lesions include ascites and peritoneal thickening, which are not measurable according to RECIST 1.1.

‡Patients who have a CA-125 response that occurs more than 28 days from PD according to RECIST 1.1 are considered a PR, according to best response, but PD if the RECIST 1.1 PD is within 28 days (including) of CA-125 response.

§The protocol should specify the minimum time interval between 2 measurements for classification as stable disease.

Signature Page

Approval with eSignature	[redacted] Clinical Development 11-Apr-2024 03:07:53 GMT+0000

Approved Date 4/10/2024