BeiGene

STATISTICAL ANALYSIS PLAN

Study Protocol Number:	BGB-A317-3111-10188-101
Study 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
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse Event
BLRM	Bayesian logistic regression model
BPH	Bayesian proportional hazard model
CLL	chronic lymphocytic leukemia
CR	complete response
DCR	disease control rate
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
FL	follicular lymphoma
imAE	immune-mediated adverse event
iwCLL	International Workshop on CLL
MCL	mantle cell lymphoma
MTD	maximum tolerated doses
MZL	marginal zone lymphoma
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PR	partial response
PK	pharmacokinetic(s)

RECIST	Response Evaluation Criteria in Solid Tumors
RDFE	recommended Phase 2 dose
R/R	relapsed/refractory
SLL	small lymphocytic lymphoma
TEAE	treatment-emergent adverse event
TTR	time to response

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for BGB-A317-3111-10188-101: 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. The focus of this SAP is for the planned analysis specified in the study protocol.

2. STUDY OVERVIEW

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:

- 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 5 parts:

- Part A, a dose-escalation phase to determine the MTD/RDFE of BGB-10188 monotherapy
- Part B, a dose-escalation phase to determine the MTD/RDFE of BGB-10188 in combination with zanubrutinib
- Part C, a dose-expansion phase for evaluation of BGB10188 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
- 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).

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 enroll patients.

The study design schematic is presented in Figure 1 in protocol. A total of approximately 84 patients (excluding patients for China verification parts) will 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. Approximately 30 to 50 patients with PROC that have progressed on/after prior anti-tumor treatment and CPI naive 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. The study design is presented in Figure 2 in protocol.

3. STUDY OBJECTIVES

3.1. Primary Objective

Part A: BGB-10188 monotherapy dose escalation in patients with mature B-cell malignancies

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

Part B: BGB 10188 + zanubrutinib dose escalation in patients with relapsed/refractory (R/R) follicular lymphoma, R/R mantle cell lymphoma, or R/R diffuse large B-cell lymphoma

- 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

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

- To evaluate the preliminary antitumor activity of BGB10188 in combination with zanubrutinib as measured by investigator-assessed overall response rate

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

Part E: BGB 10188 + tislelizumab dose expansion in patients with platinum-resistant ovarian cancer

- 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

3.2. Secondary Objective

Part A: BGB 10188 monotherapy dose escalation in patients with mature B-cell malignancies

- To evaluate the preliminary antitumor activity of BGB10188 monotherapy as measured by investigator-assessed overall response rate
- To characterize the pharmacokinetic profiles of BGB10188 as monotherapy

Part B: BGB 10188 + zanubrutinib dose escalation in patients with relapsed/refractory (R/R) follicular lymphoma, R/R mantle cell lymphoma, or R/R diffuse large B-cell lymphoma

- To evaluate the preliminary antitumor activity of BGB10188 in combination with zanubrutinib as measured by investigator-assessed overall response rate, duration of response, and time to response
- To characterize the pharmacokinetic profiles of BGB10188 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

- To evaluate the preliminary antitumor activity of BGB10188 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 BGB10188 in combination with zanubrutinib
- To characterize the pharmacokinetic profiles of BGB10188 in combination with zanubrutinib

Part D: BGB 10188 + tislelizumab dose escalation in patients with advanced solid tumors

- To evaluate the preliminary antitumor activity of BGB10188 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 BGB10188 in combination with tislelizumab

Part E: BGB 10188 + tislelizumab dose expansion in patients with platinum-resistant ovarian cancer

- 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 BGB10188 in combination with tislelizumab as measured by locally-assessed carcinoma antigen-125 (CA-125) response rate per Gynecological Cancer Intergroup (GCIG) for CA-125 changes.
- To characterize the pharmacokinetic profiles of BGB10188 in combination with tislelizumab

3.3. Exploratory Objective

Part A: BGB 10188 monotherapy dose escalation in patients with mature B-cell malignancies

- To explore relationships between BGB10188 concentrations and corrected QTcF intervals
- To characterize the pharmacodynamic profiles of BGB10188 after a single dose and at steady state
- To explore the relationships between biomarkers and mechanisms of resistance and preliminary antitumor activity of BGB10188 monotherapy

Part B: BGB 10188 + zanubrutinib dose escalation in patients with relapsed/refractory (R/R) follicular lymphoma, R/R mantle cell lymphoma, or R/R diffuse large B-cell lymphoma

- To characterize the pharmacokinetic profile of zanubrutinib when given in combination with BGB10188
- To characterize the pharmacodynamic profiles of BGB10188 in combination with zanubrutinib
- To explore the relationships between biomarkers and mechanisms of resistance and preliminary antitumor activity of BGB10188 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

- To evaluate the preliminary antitumor activity of BGB10188 in combination with zanubrutinib as measured by overall survival
- To explore the relationships between biomarkers and mechanisms of resistance and preliminary antitumor activity of BGB10188 in combination with zanubrutinib at the RDFE

- To characterize the PK profile of zanubrutinib when given in combination with BGB10188
- To characterize the pharmacodynamic profiles of BGB10188 in combination with zanubrutinib at the RDFE

Part D: BGB 10188 + tislelizumab dose escalation in patients with advanced solid tumors

- To assess host immunogenicity to tislelizumab in combination with BGB10188
- To characterize the pharmacodynamic profiles of BGB10188 in combination with tislelizumab
- To explore the relationships between biomarkers and mechanisms of resistance and preliminary anticancer activity of BGB10188 in combination with tislelizumab

Part E: BGB 10188 + tislelizumab dose expansion in patients with platinum-resistant ovarian cancer

- To assess host immunogenicity to tislelizumab in combination with BGB10188
- To characterize the pharmacodynamic profiles of BGB10188 in combination with tislelizumab at the RDFE
- To explore the relationships between biomarkers and mechanisms of resistance and preliminary anticancer activity of BGB10188 in combination with tislelizumab at the RDFE

4. STUDY ENDPOINTS

4.1. Primary Endpoint(s)

Part A: BGB 10188 Monotherapy

- The RDFE of BGB10188 monotherapy in hematologic malignancies.
- The incidence and severity according to NCI-CTCAE v5.0 of TEAEs, SAEs, and AEs leading to discontinuation of BGB10188

Part B: BGB 10188 + zanubrutinib dose escalation

- The RDFE of BGB10188 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 BGB10188 in combination with zanubrutinib

Part C: BGB 10188 + zanubrutinib dose expansion

- 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 non-Hodgkin lymphoma (Cheson et al 2014)

Part D: BGB 10188 + tislelizumab dose escalation

- The RDFE of BGB10188 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 BGB10188 in combination with tislelizumab

Part E: BGB 10188 + tislelizumab dose expansion

- ORR as assessed using RECIST V1.1 per investigator
- The incidence and severity according to NCICTCAE v5.0 of TEAEs, SAEs, and AEs leading to discontinuation of BGB10188 in combination with tislelizumab

4.2. Secondary Endpoints

Part A: BGB 10188 Monotherapy

- 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 chronic lymphocytic leukemia as per the 2018 International Workshop on Chronic Lymphocytic Leukemia guidelines (Hallek et al 2018) with modification for treatment-related lymphocytosis (Cheson et al 2012)
  - PR or better for mantle cell lymphoma, marginal zone lymphoma, follicular lymphoma, and small lymphocytic lymphoma as per the Lugano Classification for non-Hodgkin lymphoma (Cheson et al 2014)
- PK characteristics of BGB10188 including plasma concentrations of BGB10188 as a function of time and PK parameters for single (first) dose and multiple doses

Part B: BGB 10188 + zanubrutinib dose escalation

- Secondary antitumor endpoints as determined by investigator per the Lugano Classification for non-Hodgkin lymphoma (Cheson et al 2014) are as follows:
  - ORR defined by disease type as the proportion of patients achieving partial response or better for mantle cell lymphoma, follicular lymphoma, and diffuse large B-cell lymphoma
  - 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.
  - Time to response (TTR) defined as the time from treatment initiation to the first documentation of response.
- PK characteristics of BGB10188 including plasma concentrations as a function of time and PK parameters for single (first) dose and multiple doses

Part C: BGB 10188 + zanubrutinib dose expansion

- Secondary antitumor endpoints as determined by investigator per the Lugano Classification for non-Hodgkin lymphoma (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 BGB10188 + zanubrutinib
- PK characteristics of BGB10188 including plasma concentrations as a function of time and PK parameters for single (first) dose and multiple doses

Part D: BGB 10188 + tislelizumab dose escalation

- ORR, DOR, DCR, and TTR as assessed using RECIST V1.1
- PK characteristics of BGB10188 in combination with tislelizumab including plasma concentrations of BGB10188 as a function of time and PK parameters for single (first) dose and multiple doses

Part E: BGB 10188 + tislelizumab dose expansion

- DOR, PFS, DCR, CBR, and TTR as assessed using RECIST V1.1

- CA-125 response rate per GCIG as measured by investigator
- PK characteristics of BGB10188 in combination with tislelizumab including plasma concentrations of BGB10188 as a function of time and PK parameters for single (first) dose and multiple doses

4.3. Exploratory Endpoints

Part A: BGB 10188 Monotherapy

- Correlation between BGB10188 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 BGB10188
- 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 BGB10188 monotherapy in the evaluated disease types.

Part B: BGB 10188 + zanubrutinib dose escalation

- 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 BGB10188 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 BGB10188.

Part C: BGB 10188 + zanubrutinib dose expansion

- 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 BGB10188 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 BGB10188.

Part D: BGB 10188 + tislelizumab dose escalation

- Immunogenic responses to tislelizumab, evaluated through the detection of antidrug antibodies
- 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 BGB10188 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 BGB10188 in combination with tislelizumab in patients with advanced solid tumors.

Part E: BGB 10188 + tislelizumab dose expansion

- Immunogenic responses to tislelizumab, evaluated through the detection of antidrug antibodies
- 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 BGB10188 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 BGB10188 in combination with tislelizumab in patients with advanced solid tumors.

5. SAMPLE SIZE CONSIDERATIONS

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 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 1 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 1: 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: CI, confidence interval; ORR, overall response rate

6. STATISTICAL METHODS

6.1. Statistical Methods for Study Design

6.1.1. Bayesian Model-based Dose Escalation Design

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. The dose recommended by the statistical model is non-binding. The final dose-escalation recommendation will be made by the Safety Monitoring Committee based on the totality of data.

6.1.1.1 Bayesian Model-based Dose Escalation Design

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 to model the dose relationship with the DLT events in the 28-day observation period:

$$logit(p) = \log \alpha + \exp(\log \beta) \log\left(\frac{d}{d_*}\right)$$

where p is the DLT rate and d represents dose level, α, and β are parameters with prior distributions, and d_* is a reference dose set to 1000 mg. 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. The "minimally informative unimodal" beta priors are used as described in Neuenschwander et al. (2008) via specifying two quantiles of the DLT rates for the lowest and the highest dose levels. To be specific, we assume the probability of the DLT rate of the lowest dose (60 mg) that exceeds 0.333 to be 0.1 and the probability of the DLT rate of the highest dose (540 mg) that is below 0.167 to be 0.3. Assuming logistic interpolation for the other doses, a bivariate normal prior $BVN(mean_{\log(\alpha)}$=-0.26, $mean_{\log(\beta)}$ =-0.026; $sd_{\log(\alpha)}$=2.627, $sd_{\log(\beta)}$ =1.162; correlation=0.711) will be used for the two parameters log(α) and log(β) in BLRM model.

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, a different prior setting will be adopted based on the candidate dose levels considered for the combination therapy. Note that 160 mg was planned as the highest dose before the protocol amendment 4 and the prior setting was first determined based on 160 mg being the highest dose. Specifically, for combination therapy of BGB-10188 in combination with tislelizumab, to construct "minimally informative unimodal" beta priors, we assume the probability of the DLT rate of the lowest dose (20 mg) of BGB-10188 in combination with tislelizumab that exceeds 0.333 to be 0.1 and the probability of the DLT rate of highest dose (160 mg) of BGB-10188 in combination with tislelizumab that is below 0.167 to be 0.3, which would then be converted into a bivariate normal prior BVN($mean_{\log(\alpha)}$=0.118, $mean_{\log(\beta)}$ =0.175; $sd_{\log(\alpha)}$=3.722, $sd_{\log(\beta)}$ =1.007; correlation=0.749) for the two parameters in BLRM model. The reference dose used to scale 10188 doses for combination therapy is set at 500 mg. This prior setting was used for model recommendations at dose 20 mg, 40 mg, 80 mg and 160 mg. In protocol amendment 4, 320 mg was added to the dose escalation. We updated the priors by assuming the probability of the DLT rate at 320 mg of BGB-10188 in combination with tislelizumab that is below 0.167 to be 0.3. As a result, the bivariate normal prior was updated to be BVN($mean_{\log(\alpha)}$= -0.034, $mean_{\log(\beta)}$ = -0.284; $sd_{\log(\alpha)}$= 3.184, $sd_{\log(\beta)}$ =1.228; correlation= 0.713). This prior setting was used for dose recommendation at dose level of 320 mg. The reference dose used to scale 10188 doses for combination therapy is also updated to

1000 mg. After protocol amendment 5, 540 mg was added to the dose escalation. We updated the priors by assuming the probability of the DLT rate at 540 mg of BGB-10188 in combination with tislelizumab that is below 0.167 to be 0.3. As a result, the bivariate normal prior was updated to be BVN($mean_{\log(\alpha)}$= -0.44, $mean_{\log(\beta)}$ = -0.404; $sd_{\log(\alpha)}$= 2.127, $sd_{\log(\beta)}$ =1.079; correlation= 0.649). This prior setting was used for dose recommendation at dose level of 540 mg.

Bayesian Proportional Hazard Model

BPH models in the same spirit of Tighiouart et al (2014) will be used to further consider 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:

$$h(t|d) = \begin{cases} \mu_1 \cdot \exp[\beta_{PH} \cdot (\log(d) - \log(d_{min})], & t \le 4 \\ \mu_2 \cdot \exp[\beta_{PH} \cdot (\log(d) - \log(d_{min})], & 4 < t \le 8 \end{cases}$$

where $h(t|d)$ denotes hazard of DLT event of dose d at time t, μ_1 and μ_2 are baseline hazards for the two periods, respectively at a reference minimum dose d_{min} set at 5 mg. Following Tighiouart et al. (2014), the model can be re-parameterized and the prior distributions for μ_1, μ_2, and β_{PH} can be specified through the following parameters with vague priors used due to limited prior information:

- DLT rate of BGB-10188 monotherapy at d_{min} in 8 Weeks: $\rho_2 \sim uniform(0, 0.33)$;
- DLT rate ratio of BGB-10188 monotherapy at d_{min} in 28 days vs. in 8 weeks: $\frac{\rho_1}{\rho_2} \sim uniform(0, 1)$;
- MTD of BGB-10188 monotherapy: $\log(\gamma) \sim uniform(\log(20), \log(1000))$

Of note, the prior distributions for dose d_{min} indicate the probability of dose d_{min} having an overall DLT rate ≥0.333 is 0, regardless of what data is subsequently collected during the trial conduct. In order to extend an effective overdosing protection even to the lowest dose step considered in the trial, a minimum dose of 5 mg is used for d_{min}. The vague prior for the MTD with a wide range is used in order to provide reasonable chances for the minimum and maximum doses to be recommended as MTD based on data collected. 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. Specifically, we assumed $\log(\gamma) \sim uniform(\log(10), \log(500))$ for dose recommendations at dose 20 mg, 40 mg, 80 mg and 160 mg when 160 mg was planned as the highest dose level. After 320 mg was added, we relaxed the upper bound of MTD by assuming $\log(\gamma) \sim uniform(\log(10), \log(800))$, which was used for dose recommendation at dose level of 320 mg. After 540 mg was added, we relaxed the upper bound of MTD by assuming $\log(\gamma) \sim uniform(\log(10), \log(1000))$, which was used for dose recommendation at dose level of 540 mg.

6.1.1.2 Next Dose Recommendation Rules

For both Part A and Part D, next dose recommendation from the models will be a dose 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 in 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.

6.1.1.3 Escalation Phase Stopping and MTD Recommendation Rules

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

- The next dose recommended has been tested on at least 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 two immediately previous cohorts, or
- The next dose recommended has been used in three 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 6.1.1.2. 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.

6.1.2. Rule-based modified 3+3 design

Part B Combination Therapy With Zanubrutinib and Dose Verification in Chinese patients (Part A and Part D)

For the BGB-10188 dose escalation in combination with zanubrutinib in Part B and dose verification in Chinese patients in Part A and Part D, 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 at least 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 (e.g., DLTs in fewer than 2 of 6 patients) will be declared the MTD.

If less than one-third of evaluable patients (e.g., 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.

6.2. Analysis Sets

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 and had sufficient safety evaluation data. 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 BGB10188 and/or zanubrutinib (for combination therapy part). This will be the primary analysis set used for safety analyses.
- Efficacy Analysis Set is defined as all patients who received at least one medication of BGB 10188 and /or zanubrutinib (for combination therapy part) on or after C1D1. Only patients with confirmed diagnosis of the following will be included in the efficacy analysis set.
  – Part A: CLL/SLL, MZL, FL, MCL, DLBCL

  - Part B: FL, MCL, DLBCL

- PK Analysis Set is defined as all patients who had ≥ 1 postdose plasma concentration and no major protocol deviation affecting PK.

Part D and Part E

- DLT-Evaluable Set is defined as all patients who received ≥ 75% of the scheduled dose of BGB10188, ≥ 75% of the scheduled dose of tislelizumab during the first 28day treatment cycle and had sufficient safety evaluation. 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 BGB10188 will also be considered evaluable. DLT-Evaluable Set is for Part D only.
- Safety Analysis Set is defined as all patients who received at least one medication of BGB10188 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 in part D will be the primary analysis set used for efficacy analyses. 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.
- The PK Analysis Set is defined as all patients who had ≥ 1 postdose plasma concentration and no major protocol deviation affecting PK.

6.3. Multiplicity Adjustment

Not applicable because no formal hypothesis testing will be conducted.

6.4. Data Analysis General Considerations

6.4.1. Definitions and Computations

Study drugs include BGB 10188, Zanubrutinib and Tislelizumab.

Study day will be calculated in reference to the date of the dose on Cycle 1 Day 1 for Part A or first dose of study drug for other parts. For assessments conducted on or after the date of first dose, the study day will be calculated as (assessment date – first dose date + 1). For assessments

conducted before the date of first dose, study day is calculated as (assessment date – first dose date). There is no study day 0. In the situation where the event date is partial or missing, the date will appear partial or missing in the listings. Study day and any corresponding durations will be presented based on the imputations specified in Appendix 1.

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

Anchor date is defined as date of C1D1 for part A and date of first dose for other parts.

New anti-cancer therapy includes systemic anti-cancer therapy(ies), radiotherapy, cancer-related procedure/surgery post treatment discontinuation, and prohibited concomitant medications and surgeries/procedures (if identified). The same definition applies to both safety (such as the TEAE definition) and efficacy analyses.

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

6.4.2. Conventions

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

- 1 year = 365.25 days. Number of years is calculated as (days/365.25) rounded up to 1 significant digit.
- 1 month = 30.4375 days. Number of months is calculated as (days/30.4375) rounded up to 1 significant digit.
- Duration of image-based event endpoints (such as PFS) will be based on the actual date the radiograph/laboratory was performed rather than the associated visit date.
- For laboratory results collected as < or >, a numeric value, 0.0000000001 will be subtracted or added, respectively, to the value.
- For by-visit observed data analyses, percentages will be calculated based on the number of patients with non-missing data as the denominator, unless otherwise specified.
- For continuous endpoints, summary statistics will include n, mean, standard deviation, median, Q1, Q3 and range (minimum and maximum).
- For discrete endpoints, summary statistics will include frequencies and percentages.

6.4.3. Handling of Missing Data

Missing data will not be imputed unless otherwise specified elsewhere in this SAP. Missing dates or partially missing dates will be imputed conservatively for adverse events and prior/concomitant medications/procedures. Specific rules for the handling of missing or partially missing dates for adverse events and prior/concomitant medications/procedures are provided in 0.

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

6.5. Patient Characteristics

6.5.1. Patient Disposition

The number (percentage) of patients enrolled, treated, discontinued from the study, reasons for discontinued from the study, and the duration of study follow-up will be summarized in the Safety Analysis Set. The number of patients who discontinued treatment and the primary reason for the end of treatment will be summarized among patients who were treated.

6.5.2. Demographic and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized using descriptive statistics in the Safety Analysis Set, including the following variables:

- Age (continuously and by categories [<65 or ≥65 years])
- Sex
- Race
- Ethnicity
- Geographic Region
- ECOG status
- Prior radiotherapy (yes vs no)
- Prior cancer-related surgery (yes vs no)

For hematologic tumors in part A, B and C, the following additional variables will be summarized:

- Cytomegalovirus test result

- Hepatitis B core antibody status
- HBV DNA status

6.5.3. Disease History

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

Parts A, B and C

disease type, disease stage at study entry, disease stage at initial diagnosis, disease status at study entry (relapsed vs. refractory), time from initial diagnosis to first dose date, bone marrow involvement.

Parts D

disease type, disease stage at study entry, metastatic disease status at study entry, time from initial diagnosis to first dose date.

Part E

Primary location, disease stage at initial diagnosis, Epithelial Type, BRCA1 mutation status, BRCA2 mutation status, HRD status, PD-L1 score, MSI status, MMR status, tumor mutational burden status, locations of metastases/recurrence at study entry.

6.5.4. Prior Anticancer Drug Therapies and Surgeries

Prior anti-cancer drug therapies will be summarized in the Safety Analysis Set. The variables include:

Prior Systemic Anti-cancer Therapies

number of prior lines of therapy, reason for discontinuation of last prior therapy, time from end of last prior therapy to first dose date, duration of last prior therapy, best overall response to the last prior therapy. For part E only, platinum-free interval (<3 months vs 3-6 months), prior PARPi (yes vs no), prior antiangiogenesis (yes vs no), prior CPI (yes vs no).

6.5.5. Prior and Concomitant Medications

Prior medications are defined as medications that started before the 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 or the initiation of a new anti-cancer therapy, whichever comes the first.

Prior and concomitant medications will be coded using the version of World Health Organization Drug Dictionary (WHO DD) drug codes Version Mar 2023 B3. They will be further classified to the appropriate Anatomical Therapeutic Chemical (ATC) code.

The number (percentage) of patients reporting prior and concomitant medications will be summarized by ATC medication class and WHO DD preferred name in the Safety Analysis Set. A listing of prior and concomitant medications will be provided.

6.5.6. Medical History

Medical History will be coded using Medical Dictionary for Regulatory Activities (MedDRA Version 26.0). The number (percentage) of patients reporting a history of any medical condition, as recorded on the CRF, will be summarized by system organ class and preferred term in the Safety Analysis Set. A listing of medical history will be provided.

6.6. Efficacy Analysis

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

6.6.1. 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% confidence interval (CI) of ORR will be constructed to assess the precision of the point estimate of ORR.

Best overall response (BOR) is defined as the best response recorded from the start of treatment until data cutoff, first documented progression, or the initiation of new anticancer treatment, whichever occurs first. The proportion for each response category (CR, CRi, nPR, PR, PR-L, SD, and progressive disease) 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) (Part C only)

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 including 25th percentile and 75th percentile will be constructed using the Brookmeyer and Crowley method (Brookmeyer and Crowley 1982). Event-free rates at selected timepoints (3, 6, 12, 18, 24 months) for PFS will be estimated using the Kaplan-Meier method with their 2 sided 95% CIs based on the Greenwood formula (Greenwood 1926). Refer to Table 1 for censoring rules.

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. Only summary statistics of DOR will be provided if a small number of responders are observed. Otherwise, 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) (Part C only)

OS is defined as the time from treatment initiation until death due to any causes. All events of deaths will be included, regardless of whether the event occurred after the discontinuation of treatment or initiation of the new anticancer therapy. 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.

6.6.2. Part D and Part E

Overall Response Rate (ORR)

ORR is defined as the proportion of patients achieving partial response or better assessed by the investigator using RECIST V1.1 and will be analyzed the same way as in Section 6.6.1.

Progression-free Survival (PFS) (Part E only)

PFS is defined as the time from treatment initiation to the date of the first documentation of progressive disease (PD) assessed by investigator using RECIST V1.1 or death, whichever occurs first, and will be analyzed the same way as in Section . The censoring rules for PFS are presented in Table 1

Table 1: Event and Censoring Rules used in PFS

Situation	Derivation	Outcome
No baseline or postbaseline disease assessments	Anchor Date	Censor
No documented disease progression or death	Date of last adequate disease assessment prior or on the date of data cutoff, initiation of new anticancer therapy, whichever comes earlier.	Censor
Disease progression or death after more than one missed assessment (defined as the no subsequent assessment for more than 20* weeks)	Date of last adequate disease assessment before missed assessments	Censor
Disease progression or death after discontinuation from treatment	Date of disease progression or death	Event
Disease progression or death after new anticancer therapy	Date of last adequate disease assessment before new anticancer therapy	Censor

+ For part D, E, adequate disease assessment is a radiologic assessment of CR, PR, SD, non-CR/non-PD or PD as determined by the reviewers; * The number of weeks is defined as two times protocol specified interval between disease assessment plus the protocol allowed window. For Part A, B, C, follow the scheduled visits in the protocol to determine whether the PD or death is after more than one missed assessment.

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 6.6.1..

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.

Clinical Benefit Rate (CBR)

CBR 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 investigator. This will be summarized similarly as ORR. Two-sided Clopper-Pearson 95% CI of DCR will be constructed. Stable disease ≥24 weeks includes all patients with a BOR of SD and a PFS time ≥ 24 weeks.

Time to Response (TTR)

TTR is defined as the time from treatment initiation to the first documentation of response (PR or better) assessed by investigator. TTR will be analyzed the same way as in Section 6.6.1.

CA-125 Response Rate (Part E only)

CA-125 response rate is defined as the proportion of patients achieving a CA-125 response according to the GCIG 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.

Other Efficacy Analyses

Exploratory endpoints, including but not limited to correlation of clinical response to BGB-10188 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.

6.7. Safety Analyses

All safety analyses will be performed by study part, dose level or tumor type, and by total based on the Safety Analysis Set. Safety and tolerability will be assessed, where applicable, by incidence, severity, and change from baseline values for all relevant parameters including AEs, laboratory values, vital signs, ECG findings and ophthalmologic examination.

6.7.1. Extent of Exposure

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

- Duration of exposure (weeks): defined as (last exposure date - first dose date or dose on C1D1 for Part A + 1)/7. For BGB-10188 and Zanubrutinib, the last exposure date is the last dose date for patients who discontinued treatment or cutoff date for ongoing patients. For Tislelizumab, the last exposure date is min (cutoff date, death date, last dose date + 20)/7 for patients who discontinued treatment or cutoff date for ongoing patients.
- Number of treatment cycles received: defined as the total number of treatment cycles in which at least one dose of the study drug is administered.

- Cumulative dose received per patient (mg): defined as the cumulative dose of the study drug during the treatment period of the study.
- Actual dose intensity (mg/day): defined as the cumulative dose received by a patient divided by the duration of exposure (day), where duration of exposure (day) = duration of exposure (weeks) × 7. For Tislelizumab, Actual dose intensity (mg/cycle) is defined as the cumulative dose received by a patient divided by the duration of exposure (day) × 21.
- Relative dose intensity (%): defined as the ratio of the actual dose intensity and the planned dose intensity.
- Duration of dose interruption: defined as the cumulative days of zero planned dose over the treatment period.
- Number (%) of patients with dose modification/dose reduction/dose interruption or infusion interruption (for Tislelizumab) and dose delay (for Tislelizumab).

6.7.2. Adverse Events

AEs will be graded by the investigators using CTCAE version 5.0. The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using MedDRA Version 26.0. Adverse events will be coded to the MedDRA lowest level term closest to the verbatim term, along with the linked MedDRA preferred term (PT) and primary system organ class (SOC).

A treatment-emergent adverse event (TEAE) is defined as an AE that had onset or increase in severity level date on or after the date of the first dose of study drug through 30 days after the study drug discontinuation (the last one for combination therapies) or the initiation of new anti-cancer therapy, whichever is earlier. Worsening of an event to Grade 5 treatment-emergent adverse event beyond Day 30 after the last dose of study drugs is also considered a treatment-emergent adverse event (if it is prior to the start of a new anticancer therapy). 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.

Only those AEs that were treatment-emergent will be included in the summary tables of TEAE. All AEs, treatment-emergent or otherwise, will be presented in patient data listings.

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

An AE overview table, including the number and percentage of patients with TEAEs, treatment-emergent serious adverse events (SAEs), TEAEs with Grade 3 or above, TEAEs that led to death, TEAEs that led to treatment discontinuation, TEAEs that led to dose reduction, TEAEs that led to dose interruption, TEAEs leading to dose delay, infusion rate decrease and infusion interruption for Tislelizumab, treatment-related version of the above categories will be provided.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by SOC, PT and the worst grade. A patient will be counted only once by the highest severity grade within an SOC and PT, even if the patient experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of patients with treatment-emergent SAEs, TEAEs with Grade 3 or above, TEAEs that led to death, TEAEs that led to treatment discontinuation, TEAEs that led to dose reduction, TEAEs that led to dose interruption, TEAEs that led to dose delay, treatment-related SAEs, treatment-related TEAEs with Grade 3 or above will be summarized by SOC and PT.

Incidence of immune-mediated adverse event (imAE), imAE with Grade 3 or above will be summarized by category and PT. The following categories of potential interest will also be analyzed.

- ALT/AST increase
- Colitis-diarrhoea
- Pneumonitis
- Rash

Adverse event of special interest (AESI) includes any treatment emergent grade 2 or higher diarrhea (preferred term: Diarrhoea) or grade 1 diarrhea lasting for more than 7 days. The AESI will bey summarized by PT and worst grade.

Patient data listings of AEs, TEAEs with Grade 3 or above, fatal AEs will be provided.

All deaths and causes of death will be summarized including those occurred during the study treatment period and those reported during the survival follow-up period after treatment completion/discontinuation.

6.7.3. Laboratory Values

Laboratory safety tests will be evaluated for selected parameters described in Table 3.

Descriptive summary statistics (n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) for selected laboratory parameters and their

changes from baseline will be summarized by visit. In Part A, B and C, all chemistry parameters and all hematology parameters listed in Table 3 will be included. In part D and E, chemistry parameters including ALT, AST, ALP, Total bilirubin, BUN and creatinine, and all hematology parameters listed in Table 3 except for eosinophil are analyzed by visit.

Laboratory parameters that are graded in NCI CTCAE Version 5.0 will be summarized by shifts from baseline CTCAE grades to maximum post-baseline grades. In the summary of laboratory parameters by grade, parameters with grading in both high and low directions will be summarized separately. Laboratory abnormalities worsen by >=2 grades from baseline for chemistry and hematology will also be summarized.

The number of patients with positive CMV test for Part A in any visits will be summarized.

In addition, Hy's law for liver abnormality will be summarized.

Patient data listings will be provided for grade 3 or higher laboratory test toxicity and HBV DNA test. Laboratory parameters graded by iwCLL (2018) for CLL patients will be presented in the data listing.

Table 3: Serum Chemistry and Hematology Laboratory Tests

Serum Chemistry	**Hematology**
Alkaline phosphatase (ALP)	Hemoglobin
Alanine aminotransferase (ALT)	Platelet counts
Aspartate aminotransferase (AST)	White blood cell count
Albumin	Neutrophil (Absolute)
Total bilirubin	Lymphocyte (Absolute)
Blood Urea Nitrogen (BUN)	Eosinophil (Absolute)
Creatinine	
Calcium	
Phosphate	
Glucose	
Lactate dehydrogenase	
Total Protein	
Potassium	

6.7.4. Vital Signs

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

6.7.5. Ophthalmologic Examination (Part D)

Patient data listings will be provided for ophthalmologic examination results.

6.7.6. Electrocardiograms (ECG)

Descriptive statistics for ECG parameters (QTcF) and changes from baseline will be presented by visit.

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

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

6.8. 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. Pharmacokinetic parameters will be determined using a standard noncompartmental method. 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.
$AUC_{(0\text{-}t)}$ (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 tmax) will be tabulated and summarized by visit/cycle. Descriptive statistics will include means, standard deviations, medians, maximum, geometric mean, and coefficient of variation (CV) % associated to the geometric mean).

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

6.9. 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.

7. INTERIM ANALYSES

No interim analysis is planned.

8. CHANGES IN THE PLANNED ANALYSIS

Not applicable

9. REFERENCES

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IMPUTATION OF MISSING OR PARTIALLY MISSING DATES

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

1. **Prior/Concomitant Medications/Procedures**

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

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

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

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

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

If start date or end date of medication is completely missing, do not impute. If the imputed of a medication end date is greater than the death date or end of study date, then set to the death date or end of study date, whichever occurs first.

2. **Adverse Events**

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

If year of the start date is missing or start date is completely missing, do not impute. Impute AE end date first if both AE start date and end date are partially missing.

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

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

- If the imputed end date > min(death date, end of study date), then set to min (death date, end of study date)

If year of the end date is missing or end date is completely missing, do not impute.

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

- If both month and day are missing and year = year of treatment start date, then set to treatment start date
- If both month and day are missing and year ≠ year of treatment start date, then set to January 01
- If day is missing and month and year = month and year of treatment start date, the set to treatment start date
- If day is missing and month and year ≠ month and year of treatment start date, the set to first of the month
- If the imputed AE start date is after AE end date (maybe imputed), then update AE start date with AE end date as final imputed AE start date

3. **Subsequent Anti-cancer Therapies**

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

- If both month and day are missing, then the imputed month and day will be 31Dec.
- If only day is missing, then the imputed day will be the last day of the month.
- If the imputed start date > min (death date, study discontinuation date, data cutoff date, start date of the next subsequent anti-cancer therapy), then set to min (death date, study discontinuation date, data cutoff date, start date of the next subsequent therapy)

If stop date of is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month
- If the imputed stop date > min (death date, study discontinuation date, data cutoff date, start date of the next subsequent anti-cancer therapy), then set to min (death date, study discontinuation date, data cutoff date, start date of the next subsequent therapy)

The (imputed) stop date must be after or equal to the (imputed)start date
If year of the start date/stop date is missing, do not impute.

4. **Prior Therapy/Diagnosis/Response to Prior Therapy**

The following rules will be applied to impute partial dates such as initial diagnosis date, initial BCLC staging date, relapse date, therapy date (start/end date), or surgery date etc.

If start date of a disease history or prior therapy is partially missing, impute as follows:

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

If end date of a disease history or prior therapy is partially missing, impute as follows:

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