STATISTICAL ANALYSIS PLAN

Study Protocol Number:	AdvanTIG-105 (BGB-900-105)
Study Protocol Title:	Phase 1/1b Study Investigating Safety, Tolerability, Pharmacokinetics and Preliminary Antitumor Activity of Anti-TIGIT Monoclonal Antibody BGB-A1217 in Combination with Anti-PD-1 Monoclonal Antibody Tislelizumab (BGB-A317) in Patients with Unresectable Locally Advanced or Metastatic Solid Tumors
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
5-FU	5-fluorouracil
ADAs	antidrug antibodies
AE	adverse event
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BOR	best overall response
CD	cluster of differentiation
C_{max}	maximum observed plasma concentration
CPI	Checkpoint inhibitor
CR	complete response
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EAC	esophageal adenocarcinoma
EDC	electronic data capture (system)
EOT	End-of-Treatment (Visit)
ESCC	esophageal squamous cell carcinoma
ES-SCLC	extensive-stage small cell lung cancer
G/GEJ	Gastric or gastroesophageal junction
HNSCC	head and neck squamous cell carcinoma
imAE	immune-mediated adverse event
MAD	maximum administered dose
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NSCLC	non-small cell lung cancer
ORR	overall response rate
PD	progressive disease
PD-1	programmed cell death protein-1
PD-L1	programmed cell death protein-ligand 1

Abbreviation	Definition
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SCLC	small cell lung cancer
SMC	Safety Monitoring Committee
TEAE	treatment-emergent adverse event
TIGIT	T-cell immunoreceptor with Ig and ITIM domains
t_{max}	time to maximum plasma concentration
vCPS	visually-estimated Combined Positive Score

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 study BGB-900-105 (AdvanTIG-105): Phase 1/1b study investigating safety, tolerability, pharmacokinetics (PK) and preliminary antitumor activity of anti-TIGIT monoclonal antibody ociperlimab (BGB-A1217) in combination with anti-PD-1 monoclonal antibody tislelizumab (BGB-A317) in patients with unresectable locally advanced or metastatic solid tumors. The focus of this SAP is for the planned analysis specified in the study protocol. The analysis details for Pharmacodynamics, Pharmacogenomics and Biomarker are not described within this SAP. Separate analysis plans will be completed if needed.

2. STUDY OVERVIEW

2.1. Study design

Study BGB-900-105 (AdvanTIG-105) is an open-label and multicenter study to evaluate the safety, tolerability, pharmacokinetics and preliminary antitumor activity of anti-TIGIT monoclonal antibody ociperlimab (BGB-A1217) in combination with anti-PD-1 monoclonal antibody tislelizumab (BGB-A317) with or without chemotherapy in patients with unresectable locally advanced or metastatic solid tumors.

This study includes both Phase 1 and Phase 1b stages. Phase 1 includes two sessions, dose escalation in Australia and dose verification in China. Phase 1b is dose expansion on patients with specific tumor types. The study designs for Phase 1 and Phase 1b are presented in **Error! Reference source not found.**, Figure 2 and Figure 3, respectively.

For Phase 1 dose escalation in Australia, a modified 3+3 scheme is used for sequential cohorts of 4 increasing dose levels (50 mg, 150 mg, 450 mg and 900 mg) of ociperlimab, evaluated in combination with 200 mg of tislelizumab, to determine the maximum tolerated dose (MTD) or maximum administered dose (MAD). Except for the dose escalation DLT period, a 21-day treatment cycle is planned for all cycles thereafter. A 28-day DLT observation period will be utilized in the first cycle. A flat dose of ociperlimab will be administered intravenously as a single agent on Day 1 followed by a dose of 200 mg tislelizumab administered intravenously on Day 8. To be DLT evaluable, patients must receive ociperlimab alone on Day 1 of Cycle 1, followed by tislelizumab alone on Cycle 1 Day 8 (+ 2 days). If no DLT(s) are observed thereafter and through the completion of the initial 28-day cycle, patients would receive tislelizumab and ociperlimab sequentially on Day 29 and every 21 days (i.e., once every 3 weeks) thereafter until they meet a treatment discontinuation criterion.

Phase 1 dose verification in China will be conducted to evaluate the dose recommended from dose escalation session. Based on safety, tolerability, and PK data of dose escalation in Australia, as well as the consideration of any available efficacy and/or exploratory data, the recommended Phase 2 dose (RP2D) of ociperlimab in combination with tislelizumab is determined. At this RP2D level, ociperlimab as monotherapy or ociperlimab in combination with tislelizumab will be administered on Chinese patients once every 3 weeks to verify the safety and tolerability. The

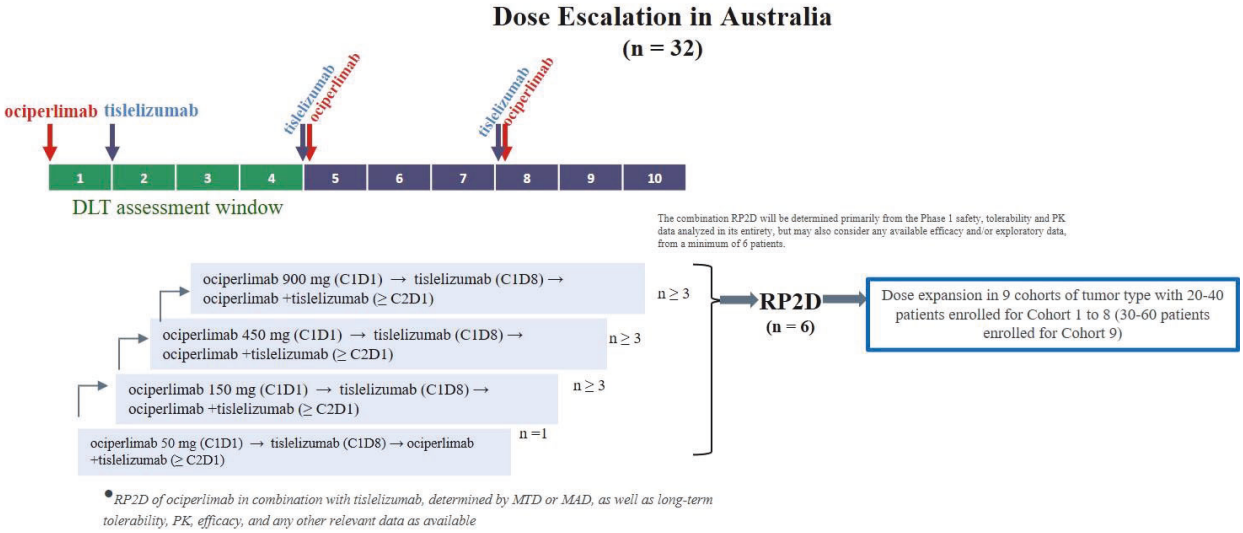
SMC will define the RP2D for Chinese patients based on the safety data from ociperlimab, combined with tislelizumab 200 mg, before Chinese patients join the Phase 1b study.

For Phase 1b dose expansion, approximately 250 to 500 evaluable patients (having measurable disease at baseline and postdose) will be enrolled into 10 different disease cohorts, including:

- **Cohort 1** (n = 20-40): Patients with metastatic squamous non-small cell lung cancer (NSCLC) will be treated with ociperlimab plus tislelizumab plus carboplatin plus paclitaxel or nab-paclitaxel.
- **Cohort 2** (n = 20-40): Patients with metastatic non-squamous NSCLC will be treated with ociperlimab plus tislelizumab plus pemetrexed plus cisplatin or carboplatin.
- **Cohort 3** (n = 20-40): Patients with metastatic NSCLC (PD-L1 positive, [TC] ≥ 1%) will be treated with ociperlimab plus tislelizumab.
- **Cohort 4** (n = 20-40): Patients with extensive-stage small cell lung cancer (SCLC) will be treated with ociperlimab plus tislelizumab plus etoposide plus cisplatin or carboplatin.
- **Cohort 5** (n = 20-40): Checkpoint inhibitor (CPI)-experienced NSCLC patients who have received prior therapies including an anti-PD-(L)1 in the most recent line of treatment will be treated with ociperlimab plus tislelizumab.
- **Cohort 6** (n = 20-40): Patients with metastatic esophageal squamous cell carcinoma (ESCC) will be treated with ociperlimab plus tislelizumab plus cisplatin plus 5-fluorouracil or paclitaxel.
- **Cohort 7** (n = 20-40): Patients with metastatic esophageal adenocarcinoma (EAC) will be treated with ociperlimab plus tislelizumab plus cisplatin plus 5-fluorouracil or paclitaxel.
- **Cohort 8** (n = 20-40): Patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC, PD-L1 positive, [vCPS] ≥ 1%) will be treated with ociperlimab plus tislelizumab.
- **Cohort 9** (n = 30-60): Patients with unresectable, locally advanced, recurrent or metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma will be treated with ociperlimab plus tislelizumab plus oxaliplatin plus capecitabine or ociperlimab plus tislelizumab plus cisplatin plus 5-fluorouracil (5-FU).
- **Cohort 10** (n=20-40 per arm, 3 dose arms): Patients with metastatic NSCLC (PD-L1 positive, [TC] ≥1%) will be treated with ociperlimab plus tislelizumab.

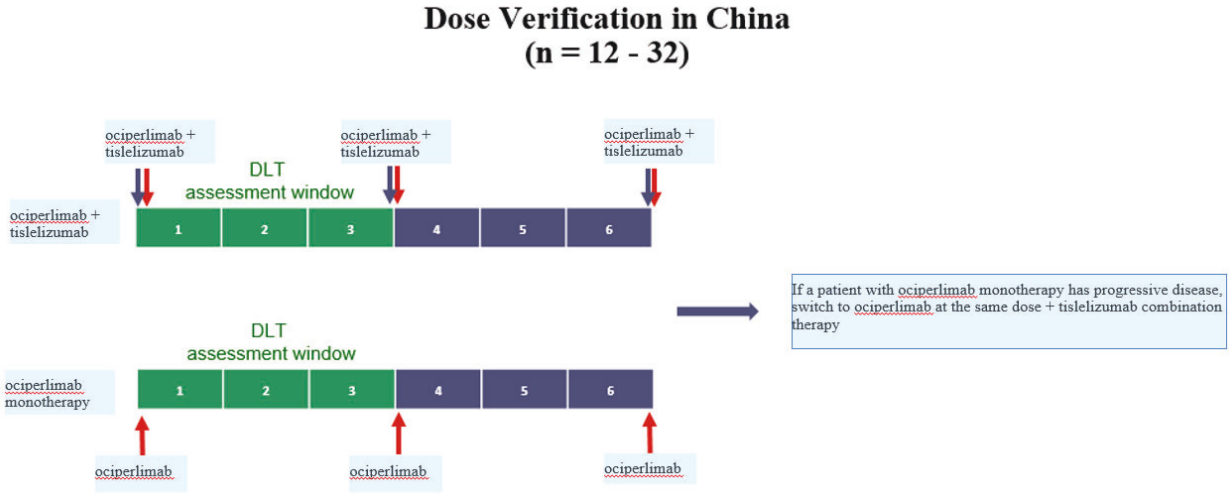
Study results will be summarized by each study session (dose escalation, dose verification and do expansion).

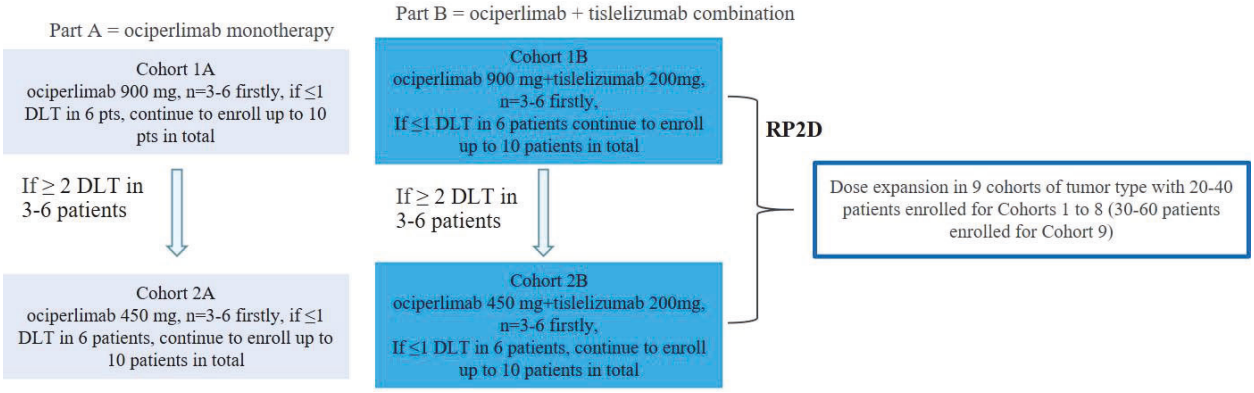
Figure 1: Study Schema for Phase 1 (Dose Escalation in Australia)



Abbreviations: C, Cycle; D, day; DLT, dose-limiting toxicity; MAD, maxima administered dose; MTD, maximal tolerated dose; PK, pharmacokinetics; RP2D, recommended Phase 2 dose.

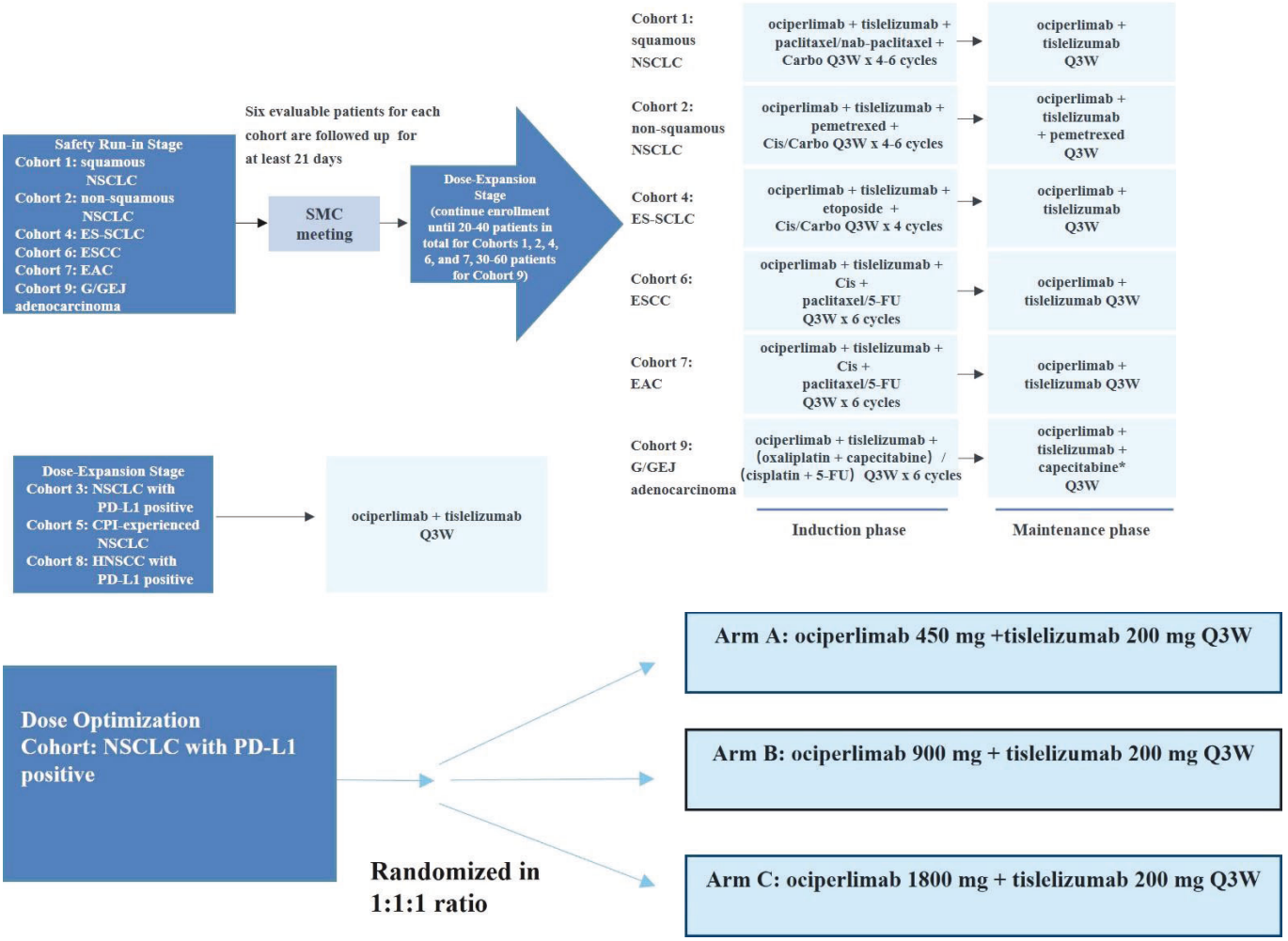
Figure 2: Study Schema for Phase 1 (Dose Verification in China)





Abbreviations: DLT, dose-limiting toxicity; mono, monotherapy; pts, patients; RP2D, recommended Phase 2 dose.

Figure 3: Study Schema for Phase 1b



Abbreviations: 5-FU, 5-fluorouracil; Carbo, carboplatin; Cis, cisplatin; EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; G/GEJ, gastric or gastroesophageal junction; NSCLC, non-small cell lung

cancer; PD-L1, programmed cell death-1 ligand; Q3W, once every 3 weeks; ES-SCLC, extensive-stage small cell lung cancer; SMC, Safety Monitoring Committee.
Note: For Cohort 9, capecitabine as optional maintenance therapy is for oxaliplatin + capecitabine regimen only.

2.2. Study assessment

Tumor imaging will be performed ≤ 28 days before the first dose of study drugs. During the study, tumor assessment will be performed approximately every 6 weeks (±7 days) from Day1 of Cycle 1 for the first 54 weeks, then every 12 weeks (±7 days) thereafter based on RECIST v1.1. If a tumor assessment is missed or conducted outside of the specified assessment window, all subsequent scans should be conducted according to the planned schedule. A patient who discontinues study drugs early for reasons other than progressive disease (PD) (e.g., toxicity) will continue to undergo tumor assessments until the patient begins a subsequent anticancer therapy, experiences PD, withdraws consent, is lost to follow-up, dies, or until the study terminates, whichever occurs first.

After initiation of study drugs, all AEs and SAEs, regardless of relationship to study drugs, will be reported until either 30 days after last dose of study drugs or initiation of subsequent anticancer therapy, whichever occurs first. Immune-mediated AEs should be reported until 90 days after the last dose of study drugs, regardless of whether or not the patient starts a subsequent anticancer therapy. All 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.

3. STUDY OBJECTIVES

Two sets of objectives are presented for Phase 1 (dose escalation and dose verification) and Phase 1b (dose expansion), respectively.

3.1. Primary Objective

Phase 1 (dose escalation + dose verification)

- To assess the safety and tolerability of ociperlimab in combination with tislelizumab in patients with advanced solid tumors
- To determine the maximum tolerated dose (MTD) or maximum administered dose (MAD) of ociperlimab in combination with tislelizumab
- To determine the recommended Phase 2 dose (RP2D) of ociperlimab in combination with tislelizumab

Phase 1b (dose expansion)

- To assess overall response rate (ORR) determined by investigator per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) for patients in each dose-expansion cohort

3.2. Secondary Objective

Phase 1 (dose escalation + dose verification)

- To assess the preliminary anticancer activity of ociperlimab in combination with tislelizumab
- To characterize the pharmacokinetics (PK) of ociperlimab in combination with tislelizumab
- To assess host immunogenicity to ociperlimab in combination with tislelizumab

Phase 1b (dose expansion)

- To evaluate disease control rate (DCR), duration of response (DOR), and progression-free survival (PFS) determined by investigator per RECIST v1.1 for patients in each dose-expansion cohort
- To further characterize the safety and tolerability of ociperlimab in combination with tislelizumab with or without chemotherapy
- To further characterize the PK of ociperlimab in combination with tislelizumab with or without chemotherapy
- To further assess host immunogenicity to ociperlimab in combination with tislelizumab with or without chemotherapy
- To evaluate the association of PD-L1 and TIGIT expression level with clinical efficacy

3.3. Exploratory Objective

Phase 1b (dose expansion)

- To assess overall survival (OS) for each dose expansion cohort

4. STUDY ENDPOINTS

Two sets of study endpoints are presented for Phase 1 (dose escalation and dose verification) and Phase 1b (dose expansion), respectively.

4.1. Primary Endpoint(s)

Phase 1 (dose escalation + dose verification)

- Adverse events (AEs) and serious AEs (SAEs) as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] version 5.0), timing, seriousness, and relationship to study drugs; physical examinations, electrocardiograms (ECGs), and laboratory assessments as needed; and AEs meeting protocol-defined DLT criteria

- MTD or MAD, as defined as the highest dose at which less than one-third of patients experienced a DLT or the highest dose administered, respectively
- RP2D of ociperlimab in combination with tislelizumab, determined by MTD or MAD, as well as long-term tolerability, PK, efficacy, and any other relevant data as available

Phase 1b (dose expansion)

- ORR, as assessed by the investigator, defined as the proportion of patients with a complete response (CR) or partial response (PR) by RECIST v1.1 for each dose expansion cohort

4.2. Secondary Endpoints

Phase 1 (dose escalation + dose verification)

- ORR, defined as above for dose escalation cohort and dose verification cohort.
- DOR, as assessed by the investigator, defined as the time from the first objective response until the first documentation of disease progression or death, whichever occurs first.
- DCR, as assessed by the investigator, defined as the proportion of patients with best overall response (BOR) per RECIST v1.1 of a CP, PR or stable disease (SD).
- Serum concentrations at specific timepoints and PK parameters (C_{max}, C_{min}, T_{max}, $AUC_{0\text{-}21d}$, $t_{1/2}$, CL, and V_{ss}, as appropriate) for ociperlimab and tislelizumab
- Immunogenic responses to ociperlimab and tislelizumab, evaluated through the detection of antidrug antibodies (ADAs)

Phase 1b (dose expansion)

- PFS, as assessed by the investigator, defined as the time from the date of first dose of study drug to the date of first documentation of disease progression per RECIST v1.1 or death, whichever occurs first.
- DOR by the investigator as defined above for each dose expansion cohort
- DCR by the investigator as defined above for each dose expansion cohort
- AEs/SAEs, physical examinations, ECGs and laboratory assessments
- Serum ociperlimab and tislelizumab concentrations at specific timepoints with or without chemotherapy
- Immunogenic responses to ociperlimab and tislelizumab, evaluated through the detection of ADAs with or without chemotherapy
- PD-L1 and TIGIT expression as the predictive biomarker for efficacy (including but not limited to ORR and PFS)

4.3. Exploratory Endpoints

Phase 1 (dose escalation + dose verification)

- Biomarkers from patient-derived tumor tissue(s) and/or blood (or blood derivatives) samples obtained before, during and/or after treatment with ociperlimab and their association with clinical efficacy.

Phase 1b (dose expansion)

- OS defined as time from the first dose of study drugs to the date of death due to any cause.
- Biomarkers from patient-derived tumor tissue(s) and/or blood (or blood derivatives) samples obtained before, during and/or after treatment with ociperlimab in combination with tislelizumab with or without chemotherapy and their association with clinical efficacy.

5. SAMPLE SIZE CONSIDERATIONS

The study plans to enroll approximately 294 to 564 patients:

- Phase 1 (dose escalation and dose verification): Approximately 44 to 64 patients
- Phase 1b (dose expansion): Approximately 250 to 500 patients in 10 prespecified tumor type cohorts (20 to 40 patients per cohort for Cohort 1 to 8, 30 to 60 patients for Cohort 9, and 20 to 40 patients for each of the 3 arms in Cohort 10)

For dose escalation in Phase 1, 32 patients should be sufficient to evaluate the safety and tolerability of increasing dose levels of ociperlimab in combination with tislelizumab per the modified 3+3 design rules. An extra 12 to 32 Chinese patients will receive ociperlimab as monotherapy or in combination with tislelizumab as dose verification. Overall, 44 to 64 patients will be enrolled in Phase 1.

6. STATISTICAL METHODS

6.1. Analysis Sets

The **Safety Analysis Set** includes all patients who received ≥ 1 dose of any study drug. This will be the analysis set for baseline characteristics, safety analyses, and efficacy analyses except for the response analyses.

The **Efficacy Evaluable Analysis Set** includes all treated patients who had measurable disease at baseline and ≥ 1 evaluable postbaseline tumor response assessment unless discontinued from any component of study treatment due to clinical PD or death within 7 weeks after first dose. This will be primary analysis set for efficacy analysis.

The **DLT Evaluable Analysis Set** includes patients who received at least 80% each of the assigned doses of ociperlimab and tislelizumab according to the treatment schedule, remained on

study during the DLT observation period and had sufficient safety evaluation or patients who experienced a DLT within the DLT observation period.

The **PK Analysis Set** includes all patients who received ≥ 1 dose of any component of study drugs per the protocol, for whom any corresponding postdose PK data are available.

The **ADA Analysis Set** includes all patients who received at least 1 dose of any component of study drugs for whom both baseline antidrug antibody result and at least 1 corresponding postbaseline antidrug antibody result are available.

6.2. Data Analysis General Considerations

6.2.1. Definitions and Computations

Study drugs include ociperlimab (BGB-A1217), tislelizumab (BGB-A317) and multiple types of chemotherapy including carboplatin, paclitaxel, nab-paclitaxel, cisplatin, pemetrexed, etoposide, 5-FU, oxaliplatin and capecitabine.

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

Baseline: Unless otherwise specified, a baseline value is defined as the last non-missing value collected before the first dose of any study drug.

All calculations and analyses will be conducted using SAS® version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina).

6.2.2. Conventions

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.
- P-values will be rounded to 4 decimal places. P-values that round to 0.0000 will be presented as '< 0.0001' and p-values that round to 1.000 will be presented as '> 0.9999'.
- Duration of imagine-based event endpoints (such as PFS) will be based on the actual date the radiograph was obtained 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, 1st quartile (Q1), 3rd quartile (Q3) and range (minimum and maximum).
- For discrete endpoints, summary statistics will include frequencies and percentages.

6.2.3. Handling of Missing Data

Missing data will not be imputed unless otherwise specified elsewhere in the SAP. Missing dates or partially missing dates will be imputed conservatively for adverse events, disease history, prior therapy, concomitant medications, and subsequent anticancer therapy. Specific rules for handling of missing or partially missing dates for adverse events and prior/concomitant medications/procedures are provided in the Appendix 1.

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

6.2.4. Multiplicity Adjustment

Not applicable.

6.3. Patient Characteristics

6.3.1. Patient Disposition

The number (percentage) of patients treated, discontinued from the study/treatment, reasons for discontinued from the study/treatment, and the duration of study follow-up will be summarized in Safety Analysis Set. The primary reason for study drug and/or the study being discontinued will be summarized according to the categories from eCRF in Safety Analysis Set.

6.3.2. Protocol Deviations

Important protocol deviation criteria will be established and patients with important protocol deviations will be identified and documented. Important protocol deviations will be summarized for all patients in the Safety Analysis Set. They will also be listed by each category. Deviation categories are not mutually exclusive. Multiple deviations within the same category are counted once per patients.

6.3.3. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized using descriptive statistics in the Safety Analysis Set, including but not limited to the following variables:

- Age (continuously and by categories [<65 or >=65 years])
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
- Sex
- Race
- Ethnicity
- Geographic Region
- ECOG Performance Status
- PD-L1 expression (Only for Phase 1b: Cohort 3, 5, 10: PD-L1 TC <1% vs PD-L1 TC>=1%; Cohort 8: PD-L1 TAP <1% vs PD-L1 TAP >=1%; Cohort 1,2,4,6,7,9: not present)
- TIGIT expression (Only for Phase 1b: Cohort 10)

6.3.4. 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.

Phase 1 (dose escalation + dose verification):

The following disease history and baseline disease characteristics will be summarized in Safety Analysis Set:

- Type of solid tumor
- Patients with metastatic disease at study entry
- Time from initial diagnosis to first dose date
- Time from diagnosis metastatic disease to first dose date

A listing of disease history will be provided.

Phase 1b (dose expansion):

The following disease history and baseline disease characteristics will be summarized in Safety Analysis Set:

- Type of solid tumor
- Patients with metastatic disease at study entry
- Disease stage at study entry
- TNM staging at study entry
- Time from initial diagnosis to first dose date

- Time from diagnosis metastatic disease to first dose date
- Histology
- Histologic grade
- EGFR mutation status
- ALK rearrangement status

A listing of disease history will be provided.

6.3.5. Prior Anticancer Systemic Therapies

The number (percentage) of patients with any prior anticancer systemic therapy, number of prior lines, time from end of last anticancer drug therapy to first dose date, time from last disease progression to first dose date, and treatment setting will be summarized in the Safety Analysis Set.

6.3.6. Prior and Concomitant Medications

Prior medications are defined as medications that stopped 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.

Prior and concomitant medications will be coded using the version of World Health Organization Drug Dictionary (WHO DD) drug codes GLOBAL B3 September 1, 2018 or higher. 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 (PT) in the Safety Analysis Set. A listing of prior and concomitant medications will be provided.

6.3.7. Medical History

Medical History will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 22.0 or higher. The number (percentage) of patients reporting a history of any medical condition, as recorded on the case report form (CRF), will be summarized by system organ class (SOC) and PT in the Safety Analysis Set. A listing of medical history will be provided.

6.3.8. Post Treatment Anticancer Therapy

Separate flags of start date of new anticancer therapy for efficacy and safety analyses are derived individually.

- As for efficacy analysis, start date of new anticancer therapy will be the earliest date of prohibited anticancer therapy taken during treatment and date of the post-treatment systemic anticancer therapy.
- The start date of new anticancer therapy in defining TEAE for safety is always the first date of new systemic anticancer therapy taken after the last study treatment.

Tumor response per RECIST v1.1 or event-driven endpoints have not been commonly used for the efficacy evaluation of traditional Chinese medicine (TCM). ORR, PFS or OS benefit of Chinese herbal medicines or Chinese patent medicines has not yet been established. Therefore, they will not be taken into account as new anticancer therapy in the efficacy and safety analyses.

Post treatment anticancer therapy is defined as the anticancer therapy started after the last dose date of study treatment. A summary of number and percentage of patients who received subsequent systematic anticancer therapy/immunotherapy by cohort will be provided based on Safety Analysis Set.

Time from last dose date to first post-treatment systemic anticancer therapy will be summarized descriptively. Patient data listings of post-treatment systemic therapy will be provided.

6.4. Efficacy Analysis

Efficacy analyses will be provided based on both the Efficacy Evaluable Analysis Set and the Safety Analysis Set. The Efficacy Evaluable Analysis Set will be the primary analysis set for response analyses; and the Safety Analysis Set will be the primary analysis set for time-to-event analyses.

6.4.1. Primary Efficacy Endpoint(s)

Phase 1 (dose escalation + dose verification):

No primary efficacy endpoint is planned for phase 1.

Phase 1b (dose expansion):

ORR by Investigators

BOR is defined as the best response recorded from the date of first dose until PD or up to start of new anticancer therapy, whichever comes first. If the first tumor assessment occurs after the new anticancer therapy, the BOR is considered as NE.

ORR is defined as the proportion of patients achieving BOR of CR or PR assessed by investigators per RECIST v1.1. Patients with no postbaseline response assessment (for any reason) will be considered as non-responders.

The proportion of patients in each response category will be presented. ORR will be summarized with a Clopper-Pearson 95% CI constructed to assess the precision of the point estimate.

6.4.2. Secondary Efficacy Endpoints

Phase 1 (dose escalation + dose verification):

ORR by Investigators

ORR by investigator is the secondary efficacy endpoint for Phase 1 and will be analyzed same as the ORR by investigator in Phase 1b.

DOR by Investigators

DOR is defined as the time from the first objective response until the first documentation of PD as assessed by the investigator per RECIST v1.1, or death, whichever occurs first. All the censoring rules for PFS will be applied to DOR. DOR will be analyzed in the responders only. The distribution of DOR, including median, Q1, Q3, and event-free rates will be estimated using the Kaplan-Meier method for each treatment group. The 95% CIs for median, Q1, and Q3 of DOR will be estimated using the method of Brookmeyer and Crowley (Brookmeyer and Crowley, 1982). And 95% CIs for event-free rates will be estimated using Greenwood's formula (Greenwood, 1926).

DCR by Investigators

DCR is defined as the proportion of patients with BOR as CR, PR, or SD assessed by investigator per RECIST v1.1. DCR assessed by investigators will be analyzed similarly to ORR.

Phase 1b (dose expansion):

DOR by Investigators

DOR by investigator is secondary efficacy endpoint in Phase 1b and will be analyzed similarly to DOR by investigator in Phase 1.

DCR by Investigators

DCR by investigator is secondary efficacy endpoint in Phase 1b and will be analyzed similarly to DCR by investigator in Phase 1.

PFS by Investigators

PFS is defined as the time from the date of first dose of study drugs to the date of first documentation of disease progression assessed by investigator per RECIST v1.1 or death, whichever occurs first. PFS will be analyzed in the Safety Analysis Set. The censoring rules for the analysis of PFS are presented in Table 1.

Kaplan-Meier methodology will be used to estimate median, Q1 and Q3 of PFS, and the event-free rates. The 95% CIs for median and other quantiles of PFS will be estimated using the method of Brookmeyer and Crowley (Brookmeyer and Crowley, 1982). The 95% CIs for event-free rates will be estimated using Greenwood's formula (Greenwood, 1926). Kaplan-Meier curves will be constructed to provide a visual description of the PFS change with time.

Table 1: Censoring Rules for Analysis of PFS per RECIST v1.1

	Derivation rules	**Outcome**
No progression at the time of data cut-off or withdrawal from study or lost to follow up	Date of last adequate radiologic assessment * prior to or on date of data cut-off or withdrawal from study or lost to follow up	Censored
New anticancer therapy started prior to disease progression or death	Date of last adequate radiological assessment before the new anticancer therapy	Censored
No baseline or postbaseline tumor assessments without death within 13 weeks after first dose	Date of first dose	Censored

No baseline or postbaseline tumor assessments with death within 13 weeks after first dose	Date of death	Event
Death or progression after more than one missed visit **	Date of last adequate radiologic assessment before missed tumor assessments	Censored
Progression documented between scheduled visits	Date of first radiologic PD assessment	Event
Death between adequate assessment visits	Date of death	Event
Death before first PD assessment	Date of death	Event

*Adequate tumor assessment is a radiologic assessment of CR, PR, SD or PD as determined by the reviewers.

**More than one missed visit is identified in the Appendix.

6.4.1. Subgroup Analyses

Subgroup analysis on key efficacy endpoints (ORR, PFS) will be conducted to explore the consistency of efficacy across a variety of subgroups, as appropriate. Subgroup variables may include but are not limited to PD-L1 expression and TIGIT expression.

6.4.2. Exploratory Efficacy Endpoints

Phase 1 (dose escalation + dose verification):

No exploratory efficacy endpoint is planned for phase 1.

Phase 1b (dose expansion):

Overall Survival

OS is defined as the time from first dose date to the documented death date for patients who died prior to or on the cutoff date. For patients who are alive by the cutoff date, OS will be censored at the last known alive date. The last known alive date will be defined as either the data cutoff date for patients who are still on treatment, or last available date showing patients alive or cut-off date whichever comes first for other alive patients.

Every effort should be made to ensure complete death dates. In the rare case, if day of death date is missing, death date is imputed as the max (last available date showing patients alive + 1, first day of month of death date). Death with missing month and/or year will not be imputed for OS analysis. The patient with imputed death date will be considered as an event for OS analysis.

The distribution of OS, including median, Q1, Q3, and event-free rates will be estimated using the Kaplan-Meier method for each treatment group. 95% CIs for median, Q1, and Q3 of OS will be estimated using the method of Brookmeyer and Crowley (Brookmeyer and Crowley, 1982).

The 95% CIs for event-free rates will be estimated using Greenwood's formula (Greenwood, 1926). Kaplan-Meier survival probabilities over time for each treatment group will be plotted.

6.5. Safety Analyses

All safety analyses will be performed by each treatment group for dose escalation, dose verification and dose expansion in Safety Analysis Set. Safety and tolerability will be assessed, where applicable, by incidence, severity, and change from baseline values for all relevant parameters including adverse events (AEs), laboratory values (e.g., hematology, clinical chemistry), vital signs, and ECG findings, etc.

6.5.1. Extent of Exposure

The following measures of the extent of exposure will be summarized for ociperlimab and tislelizumab:

- Duration of exposure (days): defined as the duration from the first dose date of study drug to the last dose date of the study drug. The duration of exposure will be calculated as (last date of exposure - date of first dose+1).
  - If patients in dose escalation phase discontinued treatment with only 1 cycle of ociperlimab (with non-missing EOT date), use min (cutoff date, death date, last dose date+27) as the 'last date of exposure' for ociperlimab.
  - For other patients discontinued treatment (with non-missing EOT date), use min (cutoff date, death date, last dose date+20) as the 'last date of exposure' for tislelizumab and ociperlimab.
  - Otherwise, if patient has treatment ongoing, using cutoff date as the 'last date of exposure' to calculate duration of exposure.
- 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.
- Total dose received per patient (mg): defined as the cumulative dose of the study drug during the treatment period of the study. It will be calculated by summing all actual doses per administration at all visits prior to or on the cutoff date.
- Actual dose intensity (ADI) (mg/cycle) of Tislelizumab: defined as the cumulative dose (mg) received by a patient divided by (last dose date – first dose date + 21)/21.
- ADI (mg/cycle) of Ociperlimab in dose escalation phase: defined as the cumulative dose (mg) received by a patient divided by (second dose cycle number -1)+ (last dose date – second dose date + 21)/21 for patients with at least two cycles of treatment or divided by 1 for patients with only one cycle of treatment.
- ADI (mg/cycle) of Ociperlimab in dose verification and dose expansion phases: defined as the cumulative dose (mg) received by a patient divided by (last dose date – first dose date + 21)/21.

- Relative dose intensity (%): defined as the ratio of the actual dose intensity and the planned dose intensity. Planned dose intensity is defined as the planned dose on study day 1 by a patient divided by the duration of exposure. The planned dose intensity for tislelizumab is 200 mg/cycle. The planned dose intensities for ociperlimab are 50 mg/cycle, 150 mg/cycle, 450 mg/cycle and 900 mg/cycle respectively for each dose level in dose escalation phase (Phase 1), 900 mg/cycle for Cohort 1A and Cohort 1B in dose verification phase (Phase 1), 900 mg/cycle for dose expansion cohorts (Phase 1b, Cohort 1 to Cohort 9), and 450 mg/cycle, 900 mg/cycle and 1800 mg/cycle for each treatment arm in Cohort 10 of Phase 1b.

The number of patients with dose modifications which includes dose missed, dose delays and inf usion interruptions and their reasons will be summarized by counts and percentages according to study drug.

Patient data listings will be provided for all dosing records, and for the above calculated summary statistics.

6.5.2. 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. Adverse events will be coded to the MedDRA (version 22.0 or higher) lowest level term closest to the verbatim term, along with the linked MedDRA preferred term (PT) and primary system organ class (SOC).

6.5.2.1. Treatment-emergent Adverse Event

A treatment-emergent adverse event (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 or initiation of the first new systemic anticancer therapy, whichever occurs first. AE start date should be collected. Any AE with missing start date will be considered as TEAE. Only those AEs that were treatment emergent will be included in summary tables of TEAE. All AEs (treatment emergent or otherwise) will be presented in patient data listings.

DLT events will be summarized by each treatment group in phase 1 (dose escalation and dose verification).

An AE overview table, including the number and percentage of patients with TEAEs, serious treatment-emergent adverse events, TEAEs with Grade 3 or above, TEAEs that led to death, TEAEs that led to treatment discontinuation, TEAEs that led to treatment modification, treatment-related TEAEs will be provided. Treatment-related AEs include those events considered by the investigator to be related to study drug(s) or with a missing assessment of the causal relationship.

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 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 serious TEAE, treatment-related TEAEs, serious treatment-

related TEAEs, TEAEs with grade 3 or above, TEAEs that led to death, TEAEs that led to treatment discontinuation, and TEAEs that led to treatment modification will be summarized by SOC and PT.

6.5.2.2. Immune-mediated Adverse Event

Immune-mediated adverse events (imAEs) are of special interest and summarized by category within a pre-defined list. The identification of immune-mediated adverse events is described in Immune-Mediated Adverse Event Identification Charter. Immune-mediated AEs will be identified from all AEs that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to 90 days after the last dose of study drug, regardless of whether the patient starts a new anticancer therapy. If an imAE occurs outside of the above-mentioned TEAE window, it will not be classified as a TEAE.

An overview table of imAE will be provided. In addition, summaries of imAEs by category and PT, grade 3 or higher imAEs, imAEs leading to death, imAEs leading to study drug discontinuation will also be presented. Patient data listings of imAEs will also be provided.

6.5.2.3. Infusion-related Reactions

For IRRs considered by investigator, an overview table and summary of incidence by SOC and PT will be provided.

6.5.2.4. Deaths

All deaths and causes of death will be summarized by dose for dose escalation phase, by cohort for dose verification phase, by cohort for tumor expansion phase from Cohort 1 to Cohort 9, by treatment arm for tumor expansion phase in Cohort 10, including those occurred during the study treatment period and those reported during the safety follow up and survival follow-up period after treatment completion/discontinuation. A patient listing of death will be provided.

6.5.3. Laboratory Values

Laboratory assessments of clinical chemistry, hematology, coagulation, and urinalysis will be conducted, of which certain elements will be collected as specified in Table 2. Parameters selected from Table 2 will be summarized as appropriate.

Descriptive statistics (n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) for laboratory parameters will be summarized as appropriate. 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 .

Laboratory parameters that are graded in NCI-CTCAE Version 5.0 will be summarized by shifts from baseline CTCAE grades to maximum postbaseline grades. In the summary of laboratory parameters by CTCAE grade, parameters with CTCAE grading in both high and low directions will be summarized separately.

Hy's Law for liver injury will also be summarized.

Box-whisker plots will be generated for parameters of interest.

Patient data listings will be provided as appropriate.

Table 2: Clinical Laboratory Assessment

Clinical chemistry	Hematology	Coagulation
Alkaline phosphatase	Hemoglobin	Activated partial thromboplastin time
Alanine aminotransferase	Platelet counts	International normalized ratio
Aspartate aminotransferase	Neutrophil count	
Albumin	Lymphocyte count	
Total bilirubin	White blood cell count	
Blood urea nitrogen		
Potassium		
Sodium		
Calcium		
Creatinine		
Glucose		
Lactate dehydrogenase		
Lipase		
Amylase		
Creatine kinase		

6.5.4. Vital Signs

The change from baseline might be summarized for all vital sign parameters except for height. Vital signs will be listed by patient and visit. Box-whisker plot will be generated for parameters of interest, as appropriate.

6.5.5. Physical Examination

Physical examination will be assessed during screening and study visits. Physical examination findings prior to first dose of study treatment will be collected in medical history, clinically significant abnormalities found in physical examination will be reported in adverse events. No separate physical examination data will be collected and reported in this study.

6.5.6. Electrocardiograms (ECG)

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 or >60 msec maximum increase from baseline

Patient listing of ECG will be provided for all ECG recordings.

6.5.7. Eastern Cooperative Oncology Group (ECOG) Performance Status

A shift table from baseline to worst postbaseline in ECOG performance status will be summarized.

6.6. Pharmacokinetic Analyses

The following analysis plan provides the framework for the analyses of the PK data. The objective is to summarize available ociperlimab and tislelizumab PK concentrations following an IV administration. The PK analyses will include only patients received ociperlimab and/or tislelizumab and with enough data to enable estimation of key parameters. Additional PK analyses (such as modeling and simulation using nonlinear mixed effects modelling) may be conducted if deemed necessary and will be described in a separate analysis plan.

6.6.1. Calculation of Pharmacokinetic Parameters

Actual dose and blood draw times will be used to calculate the PK parameters. Parameters will be listed individually and summarized by treatment group using descriptive statistics.

The following PK parameters will be calculated as appropriate for the data collected. Other PK parameters may be calculated if supported by the data.

Parameter (Units)	Definition	Method of Determination
AUC_{0-t} (μg·d/mL)	Area under the concentration versus time curve from time 0 to t hour	Calculated using the linear up/log down variant of the trapezoidal rule
AUC_{0-inf} (μg·d/mL)	AUC from zero to infinite time with extrapolation of the terminal phase	Calculated using the linear up/log down variant of the trapezoidal rule
C_{max} (μg/mL)	Maximum observed drug concentration during a dosing interval	Reported value
t_{max} (h)	Time to reach C_{max}	Actual elapsed time for observed $C_{max.}$
$t_{1/2}$ (days)	half-life	$\ln(2)/\lambda_z$, where λ_z is the first-order rate constant of drug associated with the terminal portion of the curve
CL (L/d)	Clearance	Calculated as Dose/AUC_{inf}
V_z (L)	volume of distribution during the terminal phase	Calculated as CL/λ_z, where λ_z is the first-order rate constant of drug associated with the terminal portion of the curve

6.6.2. Reporting of Pharmacokinetic Concentrations for Descriptive Statistics

The PK analyst will appropriately flag and annotate treatment of any anomalous concentrations, exclusions and any special treatment for descriptive statistics and plots. The concentration and time data will be listed individually and summarized by treatment group using descriptive statistics.

The following conventions will be used for reporting descriptive statistics for concentration data.

- PK concentrations should be reported in listings at the same level of precision as that in the source data.

- If a concentration at a given time point is below the assay quantification limit (BLQ), the concentration shall be reported as the term "BLQ" with the lower limit of quantitation (LLOQ) defined in the footnotes. BLQ values shall be treated as zero for computation of descriptive statistics. BLQ values will not be included for calculations of geometric mean and geometric coefficient of variation (CV%).
- If the calculated mean concentration is BLQ, the mean value shall be reported in outputs (such as tables) as BLQ and SD and geometric CV% shall be reported as ND (not determined). Minimum, median, and maximum may be reported.

6.6.3. Reporting of PK Parameters for Descriptive Statistics

The PK analyst will appropriately flag and annotate treatment of any anomalous PK parameters, exclusions and any special treatment for descriptive statistics.

- All the PK parameters should have at least the following summary statistics: sample size (n), mean, standard deviation (SD), coefficient of variance (CV%), median, minimum, maximum, geometric mean, geometric CV%.
- For in-text tables, Geometric mean (geometric CV%) will be the default method of reporting PK parameters. t_{max} should be presented as median, range (minimum, maximum), when presenting the summary statistics. $t_{1/2}$ should be presented as arithmetic mean, range (minimum, maximum).
- For any parameters that $n \leq 2$, SD should not be presented.
- The units for all PK parameters will be provided.
- It is recognized that the number of decimals in reported concentrations, for example: "9632.94401 ng/mL" or "9.963294401 ug/mL" are highly improbable and will be queried (since bioanalytical assays generally do not have this level of precision). Usually the first-in-human dose escalation trial will provide the numerical range of PK parameters e.g. AUC range from 10 to 10,000 ng.hr/mL and C_{max} range from 1 to 1000 ng/mL.

  In this scenario, for reporting PK parameters such as AUC and $C_{max,}$ the following guidance is provided for rounding:

  – If the numerical value is below 100 then one decimal place may be used e.g. 0.1 or 99.9.

  – For values ranging from >100, whole numbers should be used e.g. 100 or 9999.

  – If > 10,000 the clinical pharmacologist may decide on changing units e.g. from μg/ml to mg/ml.

  – For reporting times e.g. for t_{max} or $t_{1/2}$, if <1 hr use 2 decimals; time up to 24 hr should be reported to one decimal place e.g. 23.5 hr, time >24 hr should be rounded to nearest whole number e.g. 105 hr.

6.6.4. Software

For the calculations of PK parameters Phoenix® WinNonlin® Version 8 or higher (Certara, NJ. USA) will be used.

6.7. Immunogenicity Analyses

The scope of anti-drug antibodies (ADA) calculations used for characterizing clinical immunogenicity depend on the incidence and kinetics of detected (ADA). Therefore, not all parameters described below may be derived.

The immunogenicity results will be summarized using descriptive statistics by the number and percentage of subjects who develop detectable ADAs. The incidence of positive and neutralizing ADAs will be reported for ADA-evaluable subjects according to the following definitions:

- ADA-evaluable subject: Subjects with reportable non-missing baseline result and at least one reportable sample taken after drug administration during the treatment or follow-up observation period with reportable result (used for computing treatment-induced ADA incidence).
- Treatment-emergent ADA: The sum of both treatment-boosted and treatment-induced ADA positive subjects. Synonymous with "ADA Incidence".
- Treatment-induced ADA: ADA-evaluable subjects that were ADA-negative at baseline and ADA-positive following administration of biologic product.
- Treatment-boosted ADA: Baseline-positive ADA-evaluable subject with significant increases (4-fold or higher) in ADA titer after biologic drug administration. Baseline-positive ADA-evaluable subject is an ADA-evaluable subject with positive ADA result at baseline.
- Persistent ADA: Treatment-induced ADA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA positive samples (irrespective of any negative samples in between) are separated by a period of 16 weeks or longer, or, treatment-induced ADA detected in the last sampling time point, or, treatment-induced ADA detected at >=1 sampling point(s) with the last ADA-positive sample less than 16 weeks before an ADA-negative last sample.
- Transient ADA: Treatment-induced ADA that is not considered as persistent ADA.
- Neutralizing ADA: patients with positive NAb.

The individual immunogenicity results will also be listed.

Additional ADA analyses (such as the effect of immunogenicity on PK, efficacy and safety) may be conducted if deemed necessary and will be described in a separate analysis plan.

7. INTERIM ANALYSES

Not applicable.

8. CHANGES IN THE PLANNED ANALYSIS

Table 3 summarizes the major changes in the planned analyses from the statistical section of the study protocol, including the timing, rational and descriptions of the changes. The changes are all made before database lock and not based on any comparative data.

Table 3: Statistical Analysis Plan Changes

SAP version	Approval date	Change made from	Rationale of the change	Description of the change
1.0	This version	Protocol V5.0	To align with BeiGene's current standard	In the protocol, the analysis set for PFS and OS analyses is Efficacy Evaluable Analysis Set. In this SAP, the analysis set for PFS and OS analyses is Safety Analysis Set.
1.0	This version	Protocol V5.0	To align with actual enrollment practice	In the protocol, "Approximately 250 to 500 evaluable patients in 10 prespecified cohorts". In this SAP, "Approximately 250 to 500 patients in 10 prespecified cohorts". All wordings of "evaluable patients" regarding sample size considerations from protocol are replaced by wordings of "patients" regarding sample size considerations in this SAP.
1.0	This version	Protocol V5.0	To align with actual enrollment practice and BeiGene's current standard	In the section 10.8 (interim analysis) of protocol, interim analysis is planned to guide the enrollment process. In this SAP, interim analysis is not applicable. The planned interim analysis in protocol has no formal readouts and has little effect on the enrollment process in practice.
1.0	This version	Protocol V5.0	To align with BeiGene's current standard	In the protocol, "The Efficacy Evaluable Analysis Set includes all patients who received ≥ 1 dose of study drugs, have evaluable disease at baseline, and ≥ 1 evaluable postbaseline tumor response assessment unless any clinical PD or death occurred before the first postbaseline tumor assessment." In this SAP, "The Efficacy Evaluable Analysis

				Set includes all treated patients who had measurable disease at baseline and ≥ 1 evaluable postbaseline tumor response assessment unless discontinued from any treatment due to clinical PD or death within 7 weeks after first dose. This will be primary analysis set for efficacy analysis. ”
1.0	This version	Protocol V5.0	To keep an identical expression	Revised all “tumor expansion cohort” as “dose expansion cohort”, which represents cohort 1 to 10 in phase 1b.
1.0	This version	Protocol V5.0	To align with BeiGene’s current standard	In protocol, the PK Analysis Set is defined as “all patients who received ≥ 1 dose of study drug(s) and have ≥ 1 derivable PK parameter”. In this SAP, “The PK Analysis Set includes all patients who received ⩾ 1 dose of any component of study drugs per the protocol, for whom any corresponding postdose PK data are available”.
1.0	This version	Protocol V5.0	To align with BeiGene’s current standard	In protocol, the ADA Analysis Set is defined as “all patients who received ≥ 1 dose of study drug(s) and have both baseline ADA and ≥ 1 postbaseline ADA results”. In this SAP, “The ADA Analysis Set includes all patients who received at least 1 dose of any component of study drugs for whom both baseline antidrug antibody result and at least 1 corresponding postbaseline antidrug antibody result are available.”

9. REFERENCES

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics. 1982; 38:29-41.
Greenwood M. The Natural Duration of Cancer. Reports on Public health and medical subjects. 1926; 33:1-26.
Kaplan E, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958; 53:457-81.

APPENDIX 1. IMPUTATION OF MISSING OR PARTIALLY MISSING DATES

Please note: all the imputed start date should be prior to/or by last known alive date. The last known alive date only is based on complete dates without imputation.

1. Impute partial dates for concomitant medication

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

If end date of a medication/therapy/procedure 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 > death date, then set to death date

If start date of a medication/therapy/procedure 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 > min(death date, concomitant medication end date), then set to min(death date, concomitant medication end date).

If the year of start date or year of end date of a medication/therapy/procedure is missing, or the start date or end date is completely missing, do not impute.

2. 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
- If the imputed start date > min (death date, end of study date), then set to min (death date, end of study date)

3. Impute partial dates related to disease history and prior therapy (Drug, surgery/procedure, radiotherapy)

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 only one date is collected, use the start date imputation rules.

Impute end date first. If end date 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 the last day of the month
- If imputed end date > first dose date, then set to first dose date – 1 (except the prior systemic therapy for cancer, if imputed end date ≥ first dose date - 14 days, then set to first dose date – 15 days)

If start date 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 > end date, then set to the end date

If the year of start date or year of end date of a medication/therapy/procedure is missing, or the start date or end date is completely missing, do not impute.

4. Impute subsequent anti-cancer therapy

If start date of subsequent anti-cancer 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 start date > min (death date, study discontinuation date, data cutoff date, start date of the 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.

APPENDIX 2. MISSING TWO TUMOR ASSESSMENTS

Identifying two missing tumor assessments

(1) Input scheduled TA visit list for the study: 6wk-12wk-18wk-24wk-30wk-36wk-42wk-48wk-54wk-66wk-78wk-90wk…. TA as every 6 weeks for the first 54 weeks, then every 12 weeks thereafter.
(2) Identify last evaluable TA before PD or death (--LPTADT) and map it to the closest scheduled visit (--LPTADT_WK).
   a. In the event of unscheduled TA, choose the closest scheduled visit number (e.g., 6wk or 30wk) as LPTADT_WK. It can be achieved programmatically by following the classification rule (e.g., defining thresholds) depicted in Table 4 below.
   b. Otherwise, assign the scheduled visit number (assuming it is coded correctly) to LPTADT_WK
(3) Find the 2nd TA visit after LPTADT_WK according to the list in step 1 (LPTADT_WK_2)
   a. If LPTADT_WK_2+1wk (1 week TA window) < earliest of PD/death date, then censor PFS at the LPTADT
   b. Otherwise, PFS event at the earliest of PD/death date

The Threshold column is defined as the mid-point between current and next visit (except for baseline); it is the upper limit for LPTADT to be mapped to the prior scheduled assessment (step 2a above).

Table 4: scheduled tumor assessments with time window

Weeks	Scheduled week - 1	Scheduled week	Scheduled week + 1	Threshold
Baseline		Baseline		
Every 6 weeks for the first 54 weeks	Week 5	Week6	Week 7	Week 9
	Week 11	Week 12	Week 13	Week 15
	Week 17	Week 18	Week 19	Week 21
	Week 23	Week 24	Week 25	Week 27
	Week 29	Week 30	Week 31	Week 33
	Week 35	Week 36	Week 37	Week 39
	Week 41	Week 42	Week 43	Week 45
	Week 47	Week 48	Week 49	Week 51
	Week 53	Week 54	Week 55	Week 60
Every 12 weeks afterwards	Week 65	Week 66	Week 67	Week 72
	Week 77	Week 78	Week 79	Week 84
	Week 89	Week 90	Week 91	…
	…	…	…	…