BeiGene

STATISTICAL ANALYSIS PLAN

Study Protocol Number:	BGB-A317-102
Study Protocol Title:	Phase I/II Study Investigating Safety, Tolerability, Pharmacokinetics and Preliminary Antitumor Activities of Anti-PD-1 Monoclonal Antibody Tislelizumab (BGB-A317) in Chinese Patients with Advanced Solid Tumors
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2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
AUC	area under the plasma concentration and time curve
BOR	best overall response
BP	blood pressure
CBR	clinical benefit rate
CI	confidence interval
Cl	Clearance
C_{max}	maximum observed plasma concentration
CR	complete response
CRF	case report form
CRO	contract research organization
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	minimum observed plasma concentration
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
EAS	evaluable analysis set
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ENR	all patients enrolled set
GCP	Good Clinical Practice
KM	Kaplan-Meier
MedDRA®	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
ORR	objective response rate
OS	overall survival
PD	Progressive disease
PFS	progression-free survival
PK	Pharmacokinetics
PKS	PK analysis set
PR	partial response

Q2W	once every two weeks
Q3W	once every three weeks
PT	preferred term
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phases 2 dose
SAE	serious adverse events
SAF	Safety Analysis Set
SAP	statistical analysis plan
SD	stable disease
SMC	safety monitoring committee
SOC	system organ class
$T_{1/2}$	half-life
TEAE	treatment-emergent adverse event
T_{max}	time to maximum observed plasma concentration

3 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 Protocol A317-102 a "Phase I/II Study Investigating Safety, Tolerability, Pharmacokinetics and Preliminary Antitumor Activities of Anti-PD-1 Monoclonal Antibody Tislelizumab (BGB-A317) in Chinese patients with Advanced Solid Tumors". The focus of this SAP is for the planned primary, secondary and exploratory analysis after Phase I and Phase II of the study.
The analysis details for Pharmacokinetic, Pharmacodynamics, Pharmacogenomics, and Biomarker analyses are not described herein this SAP. Separate analysis plans will be completed for these specific analysis variables and attached to the clinical study report.

Reference materials for this statistical plan include the protocol BGB-A317-102 (version 2). If the protocol or case report forms are amended or updated then appropriate adjustments to the SAP may be made if they are related to the planned analyses.

The SAP described hereafter is an a priori plan. This is an open label study and the SAP will be finalized and approved before database lock. Statistical programming may occur as study data accumulate in order to have analysis programs ready at the time the study finishes.

3.1 STUDY OBJECTIVES

3.1.1 Primary Objectives

Phase I

Dose Verification study

- To assess the safety and tolerability of tislelizumab in patients with advanced solid tumors
- To determine the maximum tolerated dose (MTD), if any, and/or recommended Phase II dose (RP2D) for tislelizumab in Chinese patients

Pharmacokinetics (PK) sub-study

- To assess the PK of products derived from two manufacturing processes and scales (500L-FMP and 2000L-FMP) following the first dose of tislelizumab

  Notes: 500L-FMP indicates a final manufacturing process and scale of 500L; 2000L-FMP indicates a final manufacturing process and scale of 2000L

- To assess the safety and tolerability of tislelizumab of two manufacturing processes and scales (500L-FMP and 2000L-FMP) in patients with advanced solid tumors

Phase II

- To assess the preliminary anti-tumor activity of tislelizumab

3.1.2 Secondary Objectives

Phase I

Dose Verification Study

- To characterize the pharmacokinetics of tislelizumab
- To assess the preliminary anti-tumor activity of tislelizumab
- To assess the host immunogenicity to tislelizumab

PK sub-study

- To assess the PK of products derived from two manufacturing processes and scales (500L-FMP and 2000L-FMP) following the multiple doses of tislelizumab
- To assess the host immunogenicity to tislelizumab of two manufacturing processes and scales (500L-FMP and 2000L-FMP)
- To assess the preliminary anti-tumor activities of tislelizumab of two manufacturing processes and scales (500L-FMP and 2000L-FMP)

Phase II

- To further assess the safety and tolerability of tislelizumab
- To further assess the pharmacokinetic characteristics of tislelizumab
- To assess the host immunogenicity to tislelizumab

3.1.3 Exploratory Objectives

[redacted]

3.2 OVERALL STUDY DESIGN AND PLAN

Study Design

This study is a dose verification, PK assessment of products derived from two manufacturing processes and scales (500L-FMP and 2000L-FMP; FMP: Final Manufacturing Process) and indication expansion clinical study of monoclonal antibody tislelizumab conducted in Chinese patients with advanced solid tumors, with a purpose of exploring the safety, tolerability, pharmacokinetics and preliminary efficacy. This study is carried out on the basis of a Phase IA multi-dose and dose-escalation study in Australia. According to the preliminary results of the Phase IA clinical study in Australia, 0.5, 2, 5 and 10 mg/kg, Q2W are all tolerable doses. In addition, 2 and 5 mg/kg, Q3W have also been confirmed as tolerable doses.

This study will be carried out in two stages. Phase I is a dose verification and PK assessment of products derived from two manufacturing processes and scales (500L-FMP and 2000L-FMP, FMP = Final Manufacturing Process) study and Phase II is an indication expansion study. All patients will receive tislelizumab until they have no evidence of continued clinical benefits, unacceptable toxicity, or withdrawal of informed consent in the discretion of the investigator.

Paraffin-embedded tumor tissue will be collected for purpose of [redacted]. However, if there is clinically appropriate biopsy lesion (biopsy is a must in specific cancer types in Phase II), a fresh tumor biopsy at baseline is strongly recommended. For these patients, if possible, a biopsy for potential [redacted] after two cycles of treatment is strongly recommended. Written ICF is required for fresh tumor biopsies.

Patients will be monitored for safety, anti-tislelizumab antibodies and efficacy throughout the study. Radiological assessment of tumor-response status should be performed approximately every 9 weeks in the first year, then every 12 weeks thereafter.

Phase I

Phase I study is a multicenter and open-label study including a dose verification study and a PK sub-study of both manufacturing processes and scales of tislelizumab (500L-FMP and 2000L-FMP)

Dose Verification study (using tislelizumab produced by 500L-OMP):

3-6 patients will be enrolled firstly for DLT assessment.

- If none of the 3-6 patients experience a DLT at a pre-defined dose, enrollment will be continued until 20 patients are enrolled
- Three (3) additional patients will be enrolled if a DLT is observed in one (1) of three (3) patients; two (2) additional patients will be enrolled if a DLT is observed in one (1) of four (4) patients; and one (1) additional patient will be enrolled if a DLT is observed in one (1) of five (5) patients. No additional patients are required if a DLT is observed in one (1) of six (6) patients
- If 2 or more patients experience DLT in 3-6 patients, such dose level will considered as exceeding the MTD. All investigators will be informed of such dose level

Dose-limiting toxicity (DLT) will be assessed among evaluable patients in Cycle 1 (1-21 days) (refer to protocol section 4.2 for detailed assessment standard). An evaluable patient is defined as the patient who has received at least 80% of the first dose and completed all safety assessments required in Cycle 1, or any patient who has experienced DLT in Cycle 1.

A Safety Monitoring Committee (SMC) will be established by the sponsor and investigators. SMC will recommend RP2D based on the safety and pharmacokinetics of tislelizumab, if necessary, and decide whether to add unscheduled doses for trial.

Dose Level

According to the safety results of the dose-escalation trial on tislelizumab conducted in Australia, this study will assess the safety and pharmacokinetic characteristics of flat dose 200 mg Q3W in Chinese patients with advanced malignant solid tumors, and other doses may be further explored based on the safety result and necessity.

Among the 3-6 patients in the 200 mg Q3W cohort, if 2 or more patients experience DLT in Cycle 1, such starting dose will be considered as exceeding the MTD, and a lower dose, such as 100 mg Q3W, will be assessed in 3-6 patients.

If the dose of 200mg passes the DLT assessment, the cohort at such dose level can be expanded to 20 patients to further assess the safety, tolerability, pharmacokinetics and preliminary pharmacodynamic characteristics of tislelizumab. In order to continuously monitor safety, when a cohort has been expanded to 10 patients and >33% of them have experienced DLT within 21 days in Cycle 1, enrollment will be suspended, and an SMC meeting will be immediately held to discuss and determine whether such dose is safe.

PK sub-study: It is a parallel and multiple doses study, which analyzes the PK and safety of tislelizumab of two manufacturing processes and scales (500L-FMP and 2000L-FMP). DLT and RP2D of all patients are not assessed.

Total 48 patients (24 per arm) are planned to be enrolled to receive treatment of tislelizumab of two manufacturing processes and scales (500L-FMP and 2000L-FMP). Cycle 1 lasts for 28 days, and Cycle 2 and those thereafter last for 21 days. If there is any drop-out before the complete of the first treatment cycle (28 days) of intensive PK, additional patients will be enrolled until for each arm there are total 24 patients complete the first treatment cycle. PK, safety and preliminary anti-tumor activity are analyzed between the two arms of patients.

Phase II

In order to further assess the pharmacodynamic results of tislelizumab in Chinese patients with malignant solid tumors, once 200 mg Q3W has been confirmed as a tolerable dose in Chinese population and determined as RP2D, an indication-expansion study will be carried out among following eleven arms of indications. Because of the changes of the manufacturing processes and scales during study, tislelizumab of two manufacturing processes and scales (500L-OMP and 2000L-FMP) will be used for this Phase II study.

Arm 1: Melanoma

Arm 2: Non-small cell lung cancer (PD-L1 positive)

Arm 3: Non-small cell lung cancer (PD-L1 negative)

Arm 4: Gastric cancer

Arm 5: Esophageal cancer

Arm 6: Renal cell carcinoma

Arm 7: Urothelial carcinoma

Arm 8: MSI-H or dMMR CRC

Arm 9: Triple negative breast cancer, head and neck squamous cell carcinoma (HNSCC), small cell neuroendocrine carcinoma, or other tumors with MSI-H or dMMR

Arm 10: Nasopharyngeal carcinoma (NPC)

Arm 11: Hepatocellular carcinoma (HCC), excluding mixed hepatocellular and cholangiocellular carcinoma.

In the indication-expansion study, about 20 patients are enrolled into each arm. For tumors that are difficult to enroll, the Sponsor may early terminate the enrollment of patients in this arm. The

statistical basis for the number of patients enrolled in each arm of phase II will be specified in the statistical plan.

To fully assess the safety of tislelizumab, CRO and medical monitors from the Sponsor will regularly review the safety data, and if necessary, will convene an interim SMC meeting.

If patients with a certain kind of tumor experience significant toxicities in the dose-extension stage, the Investigator and the Sponsor will discuss and decide whether to conduct an independent study or to terminate the study in such tumor indications.

4 DETERMINATION OF SAMPLE SIZE

The sample size in the dose-validation stage in Phase I depends on the number of dose levels to be assessed and the occurrence of DLT in each cohort. The necessity of assessing additional cohorts and the corresponding samples will be determined by the safety of the dose to be investigated. It is expected that about 20 patients will be enrolled.

In Phase I PK sub-study, total 48 patients (24 per arm) are planned to be enrolled to receive treatment of tislelizumab of two manufacturing processes and scales (500L-FMP and 2000L-FMP).

Approximately 220 patients are expected to be enrolled in the indication-expansion stage in Phase II in order to perform the preliminary efficacy analysis for tislelizumab monotherapy.

5 STATISTICAL METHODS

As described in the objectives, the trial is designed to establish the safety and tolerability of tislelizumab and to assess the preliminary anti-tumor activity of tislelizumab in selected tumor types. No formal hypothesis testing is planned. Descriptive statistics and the ninety-five percent (95%) confidence interval will be presented, where applicable. The safety and efficacy data will be presented by phase, arm (only for phase II) and total unless otherwise specified.

All descriptive statistics for continuous variables will be reported using mean, standard deviation (SD), median, 25 percentile (Q1), 75 percentile (Q3), minimum (Min), maximum (Max) and n. Categorical variables will be summarized as number (percentage) of patients.

5.1 DATA ANALYSIS GENERAL CONSIDERATIONS

All efficacy analyses will be summarized with available data in the clinical database at the data cutoff. If more than one assessment are included in a time window, the assessment closest to the nominal day should be used. If there are two observations in equal distant to the nominal day the later one will be used in analyses.

5.1.1 Pooling of Centers

Data from all centers will be pooled in the analysis of this phase 1 trial.

5.1.2 Adjustments for Covariates

No adjustments for covariates are planned for primary, secondary and exploratory analyses in the study. Baseline characteristics may be used in the model as covariates as supportive exploratory analyses, if deemed necessary.

5.1.3 Multiple Comparisons/Multiplicity

No multiplicity adjustments will be made in this phase 1 trial. Two-sided 95% confidence interval will be used to describe the precision of the rate estimate whenever appropriate.

5.1.4 Examination of Subgroups

Subgroup analysis based on baseline characteristics (e.g. age group, PD-L1 expression level) in ORR will be conducted after all study data have been examined to better understand the anti-cancer activities of tislelizumab in Chinese population, if deemed necessary and when there is sufficient number of patients in the subgroup, otherwise relevant subgroups may be combined.

5.1.5 Handling of Missing Data, Drop-outs, and Outliers

At the time of primary analysis, if death or disease progression is not observed from a patient, corresponding censoring rules for OS, DOR and PFS will be followed. They are defined in Section 8.

Potential outlier values will be investigated. They will be analyzed as is in the locked database.

5.1.6 Other Considerations

Since to assess the anti-tumor activity of tislelizumab is the primary objective of the Phase II, the efficacy analyses section will refer to the Phase II in general. However, the same statistical methods will be applied in summarizing efficacy and safety data in Phase I and Phase II. Data in the Phase I will be summarized, while they will be summarized by arm in the Phase II. The primary analysis of dose expansion will be performed any time, under the discretion of the Sponsor, after mature ORR data have been obtained which is estimated to occur when all patients have completed approximately at least 6 months of treatment or discontinued due to any reason. The timings of the primary analyses are chosen such that the study endpoints can be adequately observed and results be summarized in a timely manner

5.2 STUDY ENDPOINTS

5.2.1 Primary Endpoints

Phase I

Dose Verification Study

- tislelizumab safety and tolerability: The safety of tislelizumab will be assessed throughout the study by monitoring adverse events (AEs) and serious adverse events per the NCI-CTCAE Version 4.03, physical examination, electrocardiograms and laboratory measurements

- The MTD (if any) and/or RP2D (s) for tislelizumab will be determined based on safety, tolerability, pharmacokinetics, preliminary efficacy, and other available data

Given the mechanism of tislelizumab involving immune regulation, particular attention should be paid to irAEs which include pruritus, vitiligo, pruritic rash, macular rash, hypopigmentation, and other skin disorders; hypothyroidism and hyperthyroidism, hypophysitis, pneumonitis, hepatitis, nephritis, allergic rhinitis, diarrhea, abdominal pain, fatigue, hypersensitivity and any other irAEs. Researches should be done to exclude toxic, metabolic, infectious, neoplastic or other non-drug-related etiologic causes of such events.

PK sub-study

- PK: Single-dose pharmacokinetic parameters (C_{max}, AUC_{last} and AUC_{inf}) will be assessed to evaluate the PK characteristics of tislelizumab derived from both manufacturing processes and scales
- Safety: The safety of tislelizumab will be assessed throughout the study by monitoring adverse events and serious adverse events per the NCI-CTCAE Version 4.03, physical examination, electrocardiograms, laboratory measurements

Phase II

- The objective response rate (ORR) in different tumor types will be determined by the Investigator based on RECIST Version 1.1 (ORR: complete response [CR] + partial response [PR])

5.2.2 Secondary Endpoints

Phase I

Dose Verification Study

- Pharmacokinetic evaluations: include but not limited to $AUC_{0\text{-}21\ day}$, C_{max} and T_{max}, C_{trough}, $T_{½}$, Cl and V_z
- Efficacy evaluations: ORR, CR rate, PR rate, stable disease (SD) rate, progression-free survival (PFS), overall survival (OS) and duration of response and duration of SD will be determined based on RECIST Version 1.1 criteria and the results of the Investigator evaluations
- Anti-tislelizumab antibody: immunogenic responses to tislelizumab will be assessed by monitoring the occurrence of anti-drug antibody

PK sub-study

- PK: Steady-state pharmacokinetic parameters (include but not limit to C_{trough}) will be assessed for both manufacturing processes and scales following the multiple doses of tislelizumab to evaluate the PK characteristics at steady state
- Anti-tislelizumab antibody: Immunogenic responses to tislelizumab of both manufacturing processes and scales will be assessed to evaluate the comparability of the occurrence of anti-drug antibody

- Efficacy evaluations: ORR, CR rate, PR rate, SD rate, PFS, and DOR and duration of SD will be determined by Investigator based on RECIST Version 1.1; OS will be evaluated

Phase II

- Evaluations of Efficacy: CR rate, PR rate, SD rate, PFS, duration of response, duration of SD, disease control rate (DCR) and clinical benefit rate (CBR) will be determined by investigator based on RECIST Version 1.1; OS will be evaluated
- Safety and tolerability of tislelizumab: The safety of tislelizumab will be assessed throughout the study by monitoring adverse events and serious adverse events per NCI-CTCAE Version 4.03, physical examination, electrocardiograms and laboratory assessments
- Evaluations of Pharmacokinetics: including but not limited to C_{trough}
- Anti-tislelizumab antibodies: immunogenic responses to tislelizumab will be assessed by monitoring the occurrence of anti-drug antibody (ADA)

5.2.3 Exploratory Endpoints

[redacted]

5.2.4 Definitions of Analysis Sets

All Patients Enrolled Set (ENR) includes all patients who provided informed consent for this study. The ENR analysis set will be used to summarize and describe the patient disposition unless stated otherwise.

Safety Analysis Set (SAF) includes all patients who received at least one dose of tislelizumab. The SAF analysis set will be used for all summaries (except DLT and PK analyses).

Efficacy Analysis Set (EAS) includes all patients in the SAF who had measurable disease at baseline and at least one postbaseline tumor assessment.

DLT Analysis Set (DLT) includes all patients (Phase I dose verification) who received at least 80% of tislelizumab and completed all safety assessments required in Cycle 1 or who experienced a DLT event during the DLT observation period (Cycle 1).

PK Analysis Set (PKS) includes patients in the Safety Analysis Set for whom at least one valid PK parameter can be derived for tislelizumab.

ADA Evaluable Set includes patients who received at least 1 complete dose of tislelizumab for whom both baseline ADA and at least 1 post-dose ADA result are available.

5.2.5 Patient Disposition

The number (percentage) of patients treated, discontinued from treatment, remained in treatment and survival follow-up visit will be summarized in the SAF. The primary reasons for treatment or study discontinuation will be summarized according to the categories in the CRF. Survival status (alive, death, or lost to follow-up) at the data cutoff date will be summarized using the data from the survival follow-ups.

5.2.6 Protocol Deviations

Major protocol deviation criteria will be established and patients with major protocol deviations will be identified and documented before the database lock for the primary analysis in the Phase I and Phase II.

Major protocol deviations will be summarized by phase and total in the SAF. It will also be listed by each category.

5.2.7 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized in the SAF, using descriptive statistics.

Continuous demographic and baseline variables include age, BMI (in kg/m^2), body weight (in kg), height (in cm) and vital sign parameters; categorical variables include sex, age group (<65 years, ≥65 years), and race. ECOG performance status at study entry, alcohol use and tobacco use will also be summarized.

5.2.8 Disease History

The number (percentage) of patients reporting a history of disease history and characteristics, as recorded on the CRF, will be summarized. Disease characteristics including tumor staging, tumor diagnosis, time from original histology diagnosis, time from metastatic disease, time from locally advanced disease. A patient data listing of disease history will be provided.

5.2.9 Mutation Status at Study Entry

The number (percentage) of patients in Arm 2 and Arm 3 will be summarized in expression status of PD-L1, by arm. MSI-H/dMMR status in patients with positive result in Arm 8 and in Arm 9 will also be summarized by arm. A list of status of specific markers at study entry will be provided.

5.2.10 Prior Anti-Cancer Drug Therapies and Surgeries

The number (percentage) of anti-cancer prior therapies and surgeries will be summarized for prior anti-cancer drug therapies, prior anti-cancer radiotherapy and prior anti-cancer surgeries separately. Prior anti-cancer drug therapies for advanced disease will also be summarized. Descriptive statistics may be provided as well, if needed. The therapies and surgeries with the same sequence/regimen number are counted as one prior therapy/surgery.

5.2.11 Prior and Concomitant Medications and Procedures

All investigator terms (verbatim terms) for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) drug codes. The number (percentage) of patients who took prior and concomitant medications will be summarized in the SAF by Anatomical Therapeutic Chemical (ATC) class, and WHO DD preferred term. Prior medications will be 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. A listing of prior and concomitant medications will be included in the clinical study report for this protocol.

5.2.12 Medical History

The number (percentage) of patients reporting a history of any medical condition, as recorded on the CRF, will be summarized. A patient data listing of medical will be provided. Medical History will be coded using MedDRA (version 20.1 or newer) and summaries completed by System Organ Class and Preferred term.

5.2.13 Treatment Compliance

Records of treatment compliance for each patient will be kept during the study. Clinical research associates will review treatment compliance during investigational site visits and at the completion of the study. Treatment compliance will not be summarized since the data will not be entered in the clinical database. However, dose discontinuations and dose modifications (i.e., reduction/delay/interruption/missed) will be summarized in Section 5.5.2.

5.3 EFFICACY ANALYSES

5.3.1 Primary Efficacy Analyses

Efficacy is not a primary objective of Phase I stage of this study. Objective response rate is a primary endpoint of Phase II stage. There is no formal statistical testing for the efficacy endpoints in Phase II. The efficacy analyses will be descriptive only.

Tumor assessment from investigator will be collected during the study period approximately every 9 weeks in the first 12 months and approximately 12 weeks thereafter in the simple form of five categories: CR, PR, SD, PD and NE (according to RECIST Version 1.1).

After the first documentation of response (CR or PR), an imaging test will be performed at 4 weeks later or at the next scheduled time point to confirm the response. Progressive disease (PD) suspected as pseudo-progression needs to be confirmed in a subsequent imaging at least 4 weeks later or at the next scheduled time point (but not to exceed 8 weeks), before discontinuation of study treatment.

The tables for BOR, ORR, CBR, DCR, PFS, OS and DOR will be summarized by phase, arm and total in both SAF and EAS, wherever it is applicable.

Listing of the data will be provided. If necessary, a summary of data by category will be provided.

Best Overall Response (BOR)

Best overall confirmed response reported by the investigator using RECIST 1.1, that is, CR, PR, SD, PD or NE, will be summarized.

Objective Response Rate (ORR)

The number and proportion of patients who achieve confirmed and unconfirmed objective tumor response (CR or PR) according to RECIST 1.1 will be summarized. Objective response rate will be determined along with Clopper Pearson 2-sided 95% confidence interval.

Disease Control Rate (DCR)

DCR is defined as the proportion of patients in specific tumor types reaching confirmed CR, PR and SD in accordance with RECIST V1.1 criteria. The Clopper-Pearson 2-sided 95% confidence interval will be calculated as well.

Clinical Benefit Rate (CBR)

CBR is defined as the proportion of patients in specific tumor types reaching confirmed CR, PR and durable SD (SD≥24 weeks) in accordance with RECIST V1.1 criteria. The Clopper-Pearson 2-sided 95% confidence interval will be calculated as well.

Progression Free Survival (PFS)

PFS is defined as the time from the date of first study dose to disease progression or death (whichever occurs first).

Kaplan-Meier methodology will be used to estimate median PFS and 95% confidence interval. Kaplan-Meier curves will be constructed to provide a visual description of the PFS change with time.

Overall Survival (OS)

OS is defined as the time from the date of first study dose to death. Kaplan-Meier curve will be used to estimate OS at different time points.

Duration of Response (DOR)

Duration of response for responders (CR or PR, confirmed and unconfirmed) is defined as the time interval between the date of the earliest qualifying response and the date of PD or death for any cause (whichever occurs earlier).

Kaplan-Meier curve will be used to estimate median time and 95% confidence interval for duration of response.

5.3.2 Exploratory Efficacy Analyses

[redacted]

[redacted]

5.4 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSIS

Pharmacokinetic and pharmacodynamics data will be collected in this study.

5.5 SAFETY ANALYSES

All safety analyses will be performed by dose level (only flat dose 200mg is planned) in phase I dose verification stage, PK sub-study of Phase I by two manufacturing processes and scales, and by arm in phase II and by total (combine Phase I and Phase II) based on SAF. The incidence of treatment-emergent adverse events (TEAEs, Section 5.5.3) and SAEs will be summarized. Laboratory test results, vital signs and their changes from baseline will be summarized using descriptive statistics (e.g., n, mean, standard deviation, median, Q1, Q3, minimum, maximum for continuous variables; n [%] for categorical variables. Abnormal values will be flagged.

5.5.1 Dose-Limiting Toxicity (Phase I)

DLTs are taken from the "Dose Limiting Toxicity (DLT)" form on the eCRF. All toxicities or AEs will be graded according to CTCAE v4.03. A DLT is a toxicity or AE occurring in the first cycle (21 days), which is attributable to tislelizumab and meets the criteria defined in Section 4.2 of the protocol.

All patients will be summarized by type of DLT in the dose verification stage of Phase I in the DLT Analysis Set.

5.5.2 Extent of Exposure

The tislelizumab dose information of each patient will be assessed by the following variables:

- Number of treatment cycles started equals to the count of cycles with tislelizumab
- Duration of exposure (weeks) is defined as:
  (date of last dose of tislelizumab + 21 days – date of first dose of tislelizumab)/7
- Cumulative dose (mg): the sum of all actual doses of tislelizumab, given from first to last administration
- Actual dose intensity (ADI) in mg/week is defined as:
  Cumulative dose (mg) / Duration of exposure (week)
- Relative dose intensity (RDI) in % is defined as:

$$100\times\frac{\text{ADI (mg/week)}}{\text{Planned Dose Intensity (mg/week)}}$$

where Planned dose intensity equals to 200/3 mg/week.

Number of cycles started by patient as a quantitative variable and by category (i.e., number (%) of patient receiving at least 1 cycle, at least 2 cycles etc.), duration of exposure, cumulative dose, ADI and RDI will be summarized by descriptive statistics.

The following analyses will be performed to describe tislelizumab dose modifications:
The number (percentage) of patients requiring dose interruption and dose delay due to AEs will be summarized. The cycle in which the first dose interruption/delay occurred will be summarized using descriptive statistics. Frequency of dose interruptions/delay will be summarized by categories.

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

5.5.3 Adverse Events

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

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

A treatment-emergent adverse event (TEAE) is defined as an AE that had an onset date on or after the date of first dose of study drug or a worsening in severity from baseline (pretreatment) up to 30 days following study drug discontinuation (Safety Follow-up visit) or initiation of new anticancer therapy, whichever comes first. For the tislelizumab arm, the TEAE classification also applies to irAEs that are recorded up to 90 days after discontinuation from tislelizumab, regardless of whether or not the patient starts a new anticancer therapy.

Immune-related adverse events (irAE) are of special interest in this study, TEAEs that meet the irAE criteria (consistent with IB) will be presented in summary tables and listing.

Only those AEs that are treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in patient data listings.

An overview table, including the incidence of and the number of patients with TEAEs, related TEAEs, TEAEs with grade 3 or above, serious adverse events (SAEs), deaths, and TEAEs that led to treatment discontinuation, dose reduction, dose delay, or dose interruption will be provided.

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 within a SOC and PT, even if the patient

experienced more than one TEAE within a specific SOC and PT. TEAEs with grade 3 or above will be summarized by PT in descending order.

The number (percentage) of patients with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study treatment or with missing assessment of the causal relationship.

The number (percentage) of patients with immune-related TEAEs will be summarized by SOC and PT in a separate table.

The number (percentage) of patients with TEAEs leading to death, TEAEs with grade 3 or above, SAEs, TEAEs leading to discontinuation from study drug will be summarized by MedDRA, SOC and PT in separate tables. Separate patient data listings of all AEs leading to death, treatment-related AE, grade 3 or above AEs, SAEs, AEs leading to discontinuation from study drug will be provided.

The system organ class and preferred term in the tables are listed by system organ class alphabetically first and then by decreasing order of preferred term frequency in the column of "Total" within each SOC; listed by preferred term alphabetically if the frequencies of preferred terms are the same.

5.5.4 Laboratory Values

Laboratory safety tests (serum chemistry, hematology, urinalysis, coagulation, thyroid function and immunoglobulin assessed at multiple time points, and pregnancy test assessed at screening and EOT) will be assessed in the trial.

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters listed in Table 1, the actual value and the change from baseline to each post-baseline visit and to the end of treatment will be summarized by visit using descriptive statistics. Qualitative parameters listed in Table 1 will be summarized using frequencies (number and percentage of patients), and changes from baseline to each post-baseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of patients with non-missing baseline and relevant post-baseline results.

Laboratory parameters will be categorized according to CTCAE v4.03 grades and shifts from baseline CTCAE grades to maximum and the last post-baseline grades will be assessed. Laboratory parameters will be summarized by worst post-baseline CTCAE grade as well. For the lab tests with both high and low abnormality, separate records of worst CTCAE grade (for high and low) will be generated.

Serum tumor markers will also be summarized by visit using descriptive statistics.

Table 1 Clinical Laboratory Tests

Serum Chemistry	Hematology	Coagulation	Urinalysis
Alkaline phosphatase	WBC count	Prothrombin time	pH
Alanine aminotransferase	Hematocrit	Partial thromboplastin time	Specific gravity
Aspartate aminotransferase	Hemoglobin		Glucose
Albumin	Platelet counts	International Normalized Ratio	Protein (PRO)
Total bilirubin			Ketones
Bicarbonate	RBC count		Urobilinogen
Carbon Dioxide	Neutrophil (Percentage)		
Blood Urea Nitrogen	Lymphocyte (Percentage)		Leucocyte Count (WBC)
Urea	Monocyte (Percentage)		
Creatinine	Basophil (Percentage)		Red Blood Cell (RBC)
Calcium	Eosinophil (Percentage)		Nitrite
Chloride	Neutrophil (Absolute)		
Phosphate	Lymphocyte (Absolute)		
Phosphorus	Monocyte (Absolute)		
Glucose	Basophil (Absolute)		
Lactate dehydrogenase	Eosinophil (Absolute)		
Total Protein			
Potassium	MCH		
Sodium	MCHC		
	MCV		

Abbreviations: RBC: red blood cell; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; WBC: white blood cell; pH: negative of the logarithm to base 10 of the activity of the (solvated) hydronium ion.

Table 2 Clinical Laboratory Tests (Continued)

Thyroid Function	Immunoglobulin
T3	IgG
T4	IgM
TSH	

5.5.5 Vital Signs

Descriptive statistics for vital signs parameters (i.e., resting diastolic and systolic BP, resting pulse rate, respiratory rate, temperature) and changes from baseline will be summarized by visit and treatment group.

5.5.6 Physical Examination

Physical examination parameters will be listed by visit.

5.5.7 Electrocardiograms (ECG)

ECG will be performed at the baseline and multiple time points after the start of treatment. Clinically significant abnormalities on ECG findings will be presented in a frequency table by visit and treatment group.

5.5.8 ECOG

A shift table from baseline to worst post-baseline in ECOG performance score will be summarized by phase and total. ECOG scores will be summarized by visit in phase I, phase II and total.

5.6 OTHER ANALYSES

The phase I Pharmacokinetics (PK) sub-study consists of 48 patients to be enrolled to receive treatment of tislelizumab of two manufacturing processes and scales (500L-FMP and 2000L-FMP, 24 per arm).

The objectives for the PK sub-study are:

- To assess the PK of products derived from two manufacturing processes and scales (500L-FMP and 2000L-FMP) following the first dose of tislelizumab

  Notes: 500L-FMP indicates a final manufacturing process and scale of 500L; 2000L-FMP indicates a final manufacturing process and scale of 2000L

- To assess the safety and tolerability of tislelizumab of two manufacturing processes and scales (500L-FMP and 2000L-FMP) in patients with advanced solid tumors

Details of the analysis methods for PK parameters will be described in a separate analysis plan and performed by the Pharmacokinetics group. Descriptive statistics and geometric means, and coefficients of variation (CV) for the PK parameters (C_{max}, T_{max}, C_{trough}, AUC, Cl, and Vz) will be tabulated by treatment group.

5.7 EXPLORATORY ANALYSES

Exploratory analyses may be conducted as appropriate. Any exploratory analyses that are performed will be appropriately titled/labeled as exploratory and will be clearly distinguished from planned analyses when results are reported in the Clinical Study Report.

6 INTERIM ANALYSES

No interim analysis is planned. Safety monitoring will be conducted continuously through end of treatment visit.

7 CHANGES IN THE PLANNED ANALYSES

Not applicable so far.

8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

Baseline:

Baseline is defined as the non-missing value most recently collected before the first dose.

Censoring rule for OS:

Patients who are lost to follow-up will be censored at the last date the patient was known to be alive, and patients who remained alive will be censored at the time of data cutoff.

Censoring rule for PFS:

Definition of Progression Date: Progression date is assigned to the first time at which progression can be declared.

The PFS derivation rules in this SAP follow the sensitivity analyses described in Food and Drug Administration (FDA) "Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007)" which include clinical progression with minor modification.

Censoring Rules for Analysis of Progression-Free Survival Per RECIST 1.1

Progression date based on RECIST1.1 criteria is determined as follows:

- For progression based on a new lesion, the progression date is the date of the initial detection of the new lesion, if there were multiple new lesions detected, and then the earliest date of initial detection will be used.
- If multiple assessments based on the sum of target lesion diameters are done at different times, the progression date is the date of the last radiological assessment of target lesions that shows a predefined increase of $\geq$ 20% against the nadir (the smallest sum of target lesion diameters among baseline and post-baseline tumor assessments up to the time point) in the sum of the target lesion diameters which also must demonstrate at least 5mm absolute increase.
- If progression is based on only non-target lesions, the progression date is the date of the last radiological assessment of non-target lesions for the time point that shows progression.

Table 3 shows the primary censoring rules for the derivation of PFS using RECIST 1.1 criteria based upon investigator's tumor assessment.

Table 3 Censoring Rules for Analysis of Progression-Free Survival Per RECIST 1.1

No.	Situation	Date of Progression or Censoring	Outcome
1	No baseline tumor assessments	Date of the first dose	Censored
2	Progression documented between scheduled visits	Date of first radiologic PD assessment	Progressed
3	No progression at the time of data cut-off or withdrawal from study	Date of last adequate radiologic assessment prior to or on date of data cut-off or withdrawal from study	Censored
4	New anticancer treatment started	Date of last adequate radiologic assessment prior to new anticancer treatment started	Censored
5	Death before first PD assessment	Date of death	Progressed
6	Death between adequate assessment visits*	Date of death	Progressed
7	Death or progression after more than one missed visit**	Date of last adequate radiologic assessment before missed tumor assessments	Censored

Abbreviations: CR = complete response, PD = progressive disease, PR = partial response, SD = stable disease,

* Adequate tumor assessment is a radiologic assessment of CR, PR, SD, non-CR/non-PD or PD as determined by investigators.

** If an event (PD or death) is observed:

1) If the last non-missing tumor assessment is within the 51th week from the first dose date, or no post-baseline tumor assessment, use the missing gap window as 2*9 + 1 = 19 weeks, which is 133 days, to censor the event. That is to say, if the event occurred more than or equal 133 days after the last non-missing tumor assessment or the first dose date if no post-baseline tumor assessment available, the event will be censored on the last non-missing tumor assessment date, or the first dose date if no post-baseline tumor assessment.
2) If the last non-missing tumor assessment is after the 51th week from the first dose date, use the missing gap window as 2*12 + 1 = 25 weeks, which is 175 days, to censor the event. That is to say, if the event occurred more than or equal 175 days after the last non-missing tumor assessment, the event will be censored on the last non-missing tumor assessment date.

The priority of the censoring rules is as follows:

1. If the patient had PD or death, the following sequence will be applied:
   - If a patient did not have baseline tumor assessment (No. 1), the patient will be censored on date of the first dose. However, if the patient died or had clinical progression within 49 days (6+1 weeks) after the first dose and did not receive new anticancer treatment, the date of death or clinical progression will be the PFS event date (not censored).
   - If a patient had new anticancer treatment before PD or death (No. 4), the patient will be censored on the date of the last tumor assessment prior to or on the date of new anticancer treatment.
   - If a patient missed two assessments before PD or death (No. 7), then the event will be censored on the last non-missing tumor assessment date, or the first dose date if no non-missing tumor assessment available.

     Specifically, due the fact that in most A317 studies, the scheduled tumor assessments are defined as 9 weeks in the first year, and 12 weeks after the first year, the programming logic would be proposed as

follows,

A. If an event (PD or death) is observed
   1) If the last non-missing tumor assessment is within the 51th week from the first dose date, or no post-baseline tumor assessment, use the missing gap window as 2*9 + 1 = 19 weeks, which is 133 days, to censor the event. That is to say, if the event occurred more than or equal to 133 days after the last non-missing tumor assessment or the first dose date if no post-baseline tumor assessment available, the event will be censored on the last non-missing tumor assessment date, or the first dose date if no post-baseline tumor assessment.

   2) If the last non-missing tumor assessment is after 51th week from the first dose date, use the missing gap window as 2*12 + 1 = 25 weeks, which is 175 days, to censor the event. That is to say, if the event occurred more than or equal to 175 days after the last non-missing tumor assessment, the event will be censored on the last non-missing tumor assessment date.

B. Otherwise, if no events (i.e. no PD/or death) is observed, and If no any post-baseline tumor assessments done are available, or no baseline tumor assessment (target measurement) is available, PFS will be censored to the first dose date.

C. Otherwise, i.e. post-baseline tumor assessments are available; PFS will be censored to the "last tumor assessment date" prior to the event.

- Otherwise, if a patient had an event (No. 2, No. 5, No. 6), the earliest event date will be used.

2. If a patient did not have PD or death, the censoring date will be the earliest censoring date if the patient met multiple censoring criteria (No. 1, No. 3, No. 4, No. 7).

Rules for Missing Dates

In case of dates missing in adverse event and concomitant medication collection following rules will be followed.

Adverse Events

Adverse Events with end date before first dosing date are not TEAEs. Adverse Events without end date and with incomplete start date will be considered treatment emergent if:

a. Day and month are missing and the year is equal to or after the year of the first dose date;
b. Day is missing, and the year is after the year of the first dose;
c. Day is missing and the year is equal to the year of the first dose date and the month is equal to or after the month of the first dose date;
d. Year is missing; or
e. Complete date is missing.

Concomitant Medications

Medications with end date before first dosing date are not concomitant. Medications without end date and with incomplete start date will be considered concomitant if:

a. Day and month are missing and the year is equal to or after the year of the first dose date;
b. Day is missing, and the year is after the year of the first dose;

c. Day is missing and the year is equal to the year of the first dose date and the month is equal to or after the month of the first dose date; or
d. Year is missing; or complete date is missing.

9 PROGRAMMING SPECIFICATIONS

The rules for programming derivations and dataset specifications are provided in separate documents.

10 STATISTICAL SOFTWARE

Statistical programming and analyses will be performed using SAS® (SAS Institute, Inc., Cary, NC, USA), version 9.3 or higher, and/or other validated statistical software as required.

11 MOCK TABLES, LISTINGS AND GRAPHS (TLGS)

The study TLG shells will be provided in a separate document, which will show the content and format of all tables, listings, and graphs in detail.

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