STATISTICAL ANALYSIS PLAN

Study Protocol Number:	BGB-900-104
Study Protocol Title:	A Phase 1/2 Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Preliminary Antitumor Activity of Sitravatinib as Monotherapy and in Combination With Tislelizumab in Patients With Unresectable Locally Advanced or Metastatic Hepatocellular Carcinoma or Gastric/Gastroesophageal Junction Cancer
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Antidrug Antibody
AEs	Adverse Events
ATC	Anatomical Therapeutic Chemical
CA-125	Cancer Antigen 125
CBR	Clinical Benefit Rate
CIs	Confidence Intervals
CR	Complete Response
DCR	Disease Control Rate
DOR	Duration of Response
ECG	Electrocardiograms
ECOG	Eastern Cooperative Oncology Group
GCIG	Gynecologic Cancer Intergroup
imAEs	Immune-mediated AEs
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PD-1	Programmed Cell Death Protein-1
PD-L1	Programmed Cell Death Protein-Ligand 1
PFS	Progression-Free Survival
PGx	Pharmacogenetic
PK	Pharmacokinetic(s)
PR	Partial Response
PT	Preferred Term
RECIST	Response Evaluation Criteria in Solid Tumors
SAEs	Serious Adverse Events
SD	Stable Disease
SFD	Study Follow-up Duration
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TTR	Time to Response
WHO DD	World Health Organization Drug Dictionary

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for BGB-900-104: A Phase 1/2 study to investigate the safety, tolerability, pharmacokinetics, and preliminary antitumor activity of sitravatinib as monotherapy and in combination with tislelizumab in patients with unresectable locally advanced or metastatic hepatocellular carcinoma or gastric/gastroesophageal junction cancer. This SAP is based on BGB-900-104 Protocol Amendment 4.0, dated on April 28, 2020. The focus of this SAP is for the planned final analysis specified in the study protocol. The analysis details for Pharmacodynamics, Pharmacogenomics and Biomarker are not described within this SAP.

2. STUDY OVERVIEW

2.1. Study Design

This is an open-label, multicenter Phase 1/2 clinical study for patients with histologically or cytologically confirmed unresectable locally advanced or metastatic hepatocellular carcinoma (HCC) or gastric/gastroesophageal junction (G/GEJ) cancer. All patients will receive study treatment(s) until PD, unacceptable toxicity, death, withdrawal of consent, or study termination by sponsor.

This study consists of 2 phases.

2.1.1. Phase 1 (Dose Escalation for Sitravatinib as Monotherapy and in Combination With Tislelizumab)

Two dose levels of sitravatinib as monotherapy, 80 mg once daily and 120 mg once daily, will be evaluated in patients with unresectable locally advanced or metastatic HCC or G/GEJ cancer. A modified 3 + 3 design will be used in the dose escalation. Approximately 6 to 12 DLT evaluable patients will be treated with sitravatinib as monotherapy.

The combination dose escalation of sitravatinib (80 mg once daily and 120 mg once daily; modified 3 + 3 design) with tislelizumab (200 mg once every 3 weeks, in both cohorts) will be evaluated in patients with unresectable locally advanced or metastatic HCC or G/GEJ cancer. Approximately 12 to 24 DLT evaluable patients will be treated.

DLT assessment will be performed for HCC, G/GEJ cancer respectively.

DLT Observation Period and the Modified 3 + 3 Scheme

For Phase 1 dose escalation, a 21-day DLT assessment window will be utilized for initial dose confirmation recommendations. DLTs will be assessed among evaluable patients within 21 days after the first dose of study drug(s). For dose escalation decisions, only DLTs occurring within 21 days will be evaluated.

Dose escalation in sitravatinib monotherapy or sitravatinib in combination with tislelizumab will occur in accordance with the following modified 3 + 3 dose escalation rules.

A minimum of 3 DLT evaluable patients will be initially enrolled per cohort.

- If none of the first 3 evaluable patients enrolled in a given cohort experience a DLT, dose escalation may proceed.
- If one of the first 3 evaluable patients enrolled in a given cohort experiences a DLT, additional patients (for a minimum of 6 evaluable patients) will be enrolled in that cohort.
  - If less than one third of evaluable patients in a given cohort experiences a DLT (eg, DLTs in fewer than two of 6 evaluable patients), escalation will proceed to the next higher dose level.

If a DLT is observed in at least one-third or more of evaluable patients (eg, two or more of up to 6 evaluable patients), the dose escalation will be stopped. A lower dose level or an intermediate dose level may be evaluated if recommended by the SMC.

The SMC will confirm RP2D of the monotherapy and combination treatment based on all available safety, efficacy, PK and exploratory data. Additional dose levels may be evaluated if needed. For the sitravatinib combination therapy, RP2Ds for each tumor type will be recommended by SMC based on 6 to 12 DLT evaluable patients respectively.

2.1.2. Phase 2 (Dose Expansion for Sitravatinib as Monotherapy and in Combination With Tislelizumab)

There will be a total of 4 cohorts in the study. Approximately 20 patients will be enrolled in each cohort.

Sitravatinib monotherapy

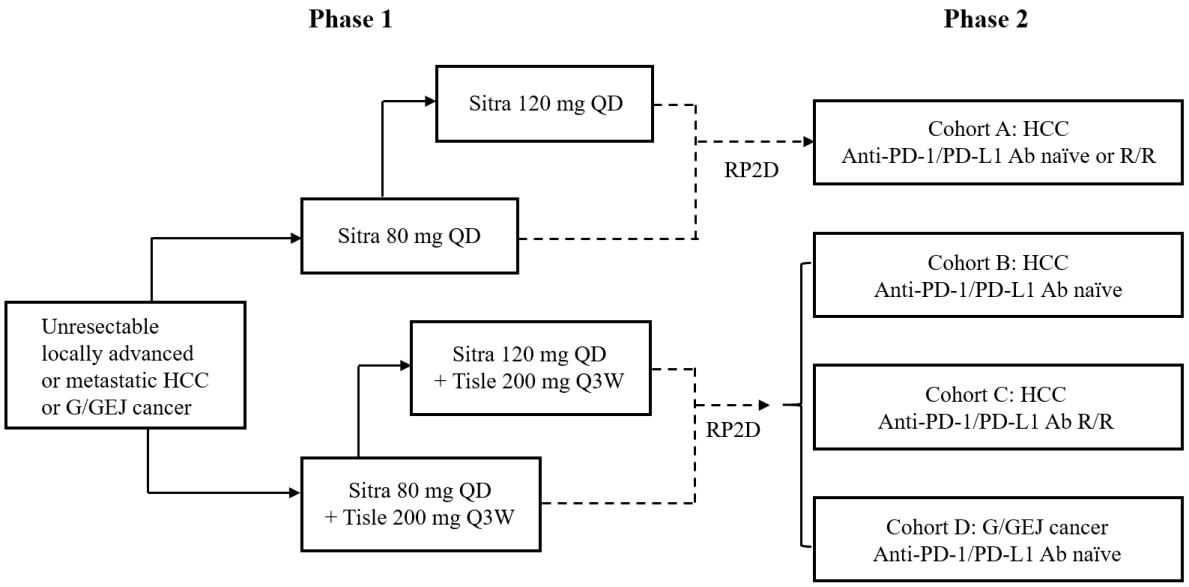
- Cohort A: Anti-PD-1/PD-L1 antibody naïve or refractory/resistant HCC

Sitravatinib in combination with tislelizumab

- Cohort B: Anti-PD-1/PD-L1 antibody naïve HCC
- Cohort C: Anti-PD-1/PD-L1 antibody refractory/resistant HCC
- Cohort D: Anti-PD-1/PD-L1 antibody naïve G/GEJ cancer

The study schema is in Figure 1. Study SchemaFigure 1.

Figure 1. Study Schema



Abbreviations: Ab, antibody; G/GEJ, gastric/gastroesophageal junction, HCC, hepatocellular carcinoma; PD-1, programmed cell death protein-1; PD-L1, programmed cell death protein ligand-1; PK, pharmacokinetic; QD, once a day; Q3W, once every 3 weeks; RP2D, recommended Phase 2 dose; R/R, refractory or resistant, Sitra, sitravatinib; SMC, Safety Monitoring Committee; Tisle, tislelizumab.
Note: The combination dose escalation may start simultaneously with the monotherapy cohort. The SMC will confirm RP2D of the monotherapy and combination treatment based on all available safety, efficacy, PK and exploratory data. Additional dose levels may be evaluated if needed. For the sitravatinib combination therapy, RP2Ds for each tumor type will be recommended by SMC based on 6 to 12 DLT evaluable patients respectively.

2.2. Study Assessments

Tumor Assessment:

Tumor assessments will be performed by investigator using Response Evaluation Criteria in Solid Tumors (RECIST) version (v) 1.1 criteria (Eisenhauer et al. 2009). Tumor imaging will be performed at baseline (within 28 days prior to the first dose of study drugs). During the study, tumor imaging will be performed approximately every 6 weeks (± 7 days) in the first 12 months and thereafter approximately every 9 weeks (± 7 days). If a patient discontinues study treatment due to any reasons other than disease progression, tumor assessments will continue to be performed as scheduled until initiation of a new anticancer therapy, disease progression, loss to follow up, withdrawal of consent, death, or until the study terminates, whichever occurs first.

Safety Assessment:

Patients will be evaluated for any adverse events (AEs) and serious adverse events (SAEs) occurring up to 30 days after the last dose of study drugs (all severity grades, per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0) or initiation of a new anticancer therapy, whichever occurs first, and immune-mediated AEs (imAEs) occurring up to 90 days after the last dose of tislelizumab regardless of initiation of a subsequent anticancer therapy. At the end of treatment, ongoing AEs considered related to study treatment will be followed until the event has resolved to baseline or ≤ Grade 1, the event is assessed by the

investigator as stable, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the AE. All drug-related SAEs will be recorded by investigator after treatment discontinuation until patient death, withdrawal of consent, or loss to follow up, whichever occurs first.

3. STUDY OBJECTIVES

3.1. Study Objective for Phase 1 (Dose Escalation)

3.1.1. Primary Objectives

- To characterize safety and tolerability of sitravatinib as monotherapy and in combination with tislelizumab
- To confirm the RP2D for sitravatinib as monotherapy and in combination with tislelizumab

3.1.2. Secondary Objectives

- To characterize the Pharmacokinetic (PK) profiles of sitravatinib after single dose and at steady state when given in combination with tislelizumab
- To assess the preliminary antitumor activity of sitravatinib as monotherapy and in combination with tislelizumab in HCC or gastric/gastroesophageal junction (G/GEJ) cancer patients

3.1.3. Exploratory Objective

- To assess PK and immunogenicity of tislelizumab when given in combination with sitravatinib

3.2. Study Objective for Phase 2 (Dose Expansion)

3.2.1. Primary Objective

- To assess the preliminary antitumor activity as indicated by ORR per Response Evaluation Criteria in Solid Tumors (RECIST) version (v) 1.1 of sitravatinib as monotherapy and in combination with tislelizumab

3.2.2. Secondary Objectives

- To assess the preliminary antitumor activity as indicated by duration of response (DOR), DCR and PFS per RECIST v1.1 as monotherapy and in combination with tislelizumab
- To characterize the safety and tolerability of sitravatinib as monotherapy and in combination with tislelizumab
- To characterize the PK profile of sitravatinib

3.2.3. Exploratory Objectives

- To assess PK and immunogenicity of tislelizumab when given in combination with sitravatinib
- To assess overall survival (OS)

4. STUDY ENDPOINTS

4.1. Primary Endpoints for Phase 1 (Dose Escalation)

4.1.1. Primary Endpoints

- Safety and tolerability will be assessed throughout the study by monitoring AEs and SAEs per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0, relevant physical examination, electrocardiograms (ECGs), and laboratory assessments as needed

4.1.2. Secondary Endpoints

- Plasma concentrations and the derived PK parameters of sitravatinib if data permit:
  - Single dose: C_{max}, time to maximum plasma concentration (T_{max}), $AUC_{0\text{-}t}$, clearance after oral administration (CL/F)
  - Repeating dose: C_{max}, C_{τ}, T_{max}, $AUC_{0\text{-}tau}$, CL/F, accumulation ratio (R_o)
- Efficacy evaluations by investigators: ORR, DOR, DCR, and PFS based on RECIST v1.1.

4.1.3. Exploratory Endpoints

- Serum concentrations of tislelizumab and anti-tislelizumab antibodies

4.2. Primary Endpoints for Phase 2 (Dose Expansion)

4.2.1. Primary Endpoint

- Objective response rate (ORR), defined as the percentage of patients whose best overall response (BOR) is CR or PR assessed by investigators per RECIST v1.1

4.2.2. Secondary Endpoints

- Duration of response (DOR), defined as the time from the first determination of an objective response until the first documentation of PD as assessed by investigator per RECIST v1.1, or death, whichever comes first
- Disease control rate (DCR), defined as the proportion of patients with BOR as CR, PR, or SD assessed by investigator per RECIST v1.1
- Progression-free survival (PFS), defined as the time from the date of first dose to the date of first documentation of PD assessed by the investigator per RECIST v1.1 or death, whichever occurs first.

- Safety and tolerability will be assessed throughout the study by monitoring AEs and SAEs per NCI-CTCAE v5.0, relevant physical examination, ECGs, and laboratory assessments as needed
- Plasma concentrations of sitravatinib predose and postdose at steady state

4.2.3. Exploratory Endpoints

- Serum concentrations of tislelizumab and anti-tislelizumab antibodies
- OS is defined as the time from date of first dose of study drug(s) to date of death due to any cause

5. SAMPLE SIZE CONSIDERATIONS

The study plans to enroll approximately 98 to 116 patients.

- Phase 1 (sitravatinib as monotherapy and in combination with tislelizumab dose escalation): Approximately 18 to 36 DLT evaluable patients with unresectable locally advanced or metastatic HCC or G/GEJ cancer will be enrolled.
- Phase 2 (sitravatinib as monotherapy and in combination with tislelizumab combination dose expansion): Approximately 80 patients will be enrolled in Phase 2 (approximately 20 patients per cohort). Enrollment into these cohorts will occur simultaneously and independent of each other. Each cohort will be evaluated separately.

Estimates of the exact 95% CI of the observed ORR for several potential outcomes using the sample size of 20 patients are provided in Table 1.

Table 1: Estimates of 95% CI of ORR With 20 Patients

Number of Observed Response	ORR	95% Exact CI
4	20%	5.7%, 43.7%
6	30%	11.9%, 54.3%
8	40%	19.1%, 63.9%
10	50%	27.2%, 72.8%
12	60%	36.1%, 80.9%

6. STATISTICAL METHODS

In general, data from phase 1 and phase 2 studies will be summarized together by indication for efficacy analysis, and by dosage, and indication separately for patient characteristic and safety analysis, unless otherwise specified. Four patients who are in phase 1 with GC/GEJC were either anti-PD-(L)1 R/R (086022-008) or took Sitravatinib monotherapy (086022-001, 086022-004,

086025-004). These four patients are not included in summary statistics by indication because of small sample size. The layout for tables by indication or by dosage is presented in Table 2 and Table 3.

Table 2: Layout for tables by indication

	Sitra HCC anti-PD-(L)1 Naïve or R/R	Sitra + Tisle HCC anti-PD-(L)1 Naïve	Sitra + Tisle HCC anti-PD-(L)1 R/R	Sitra + Tisle HCC Subtotal	Sitra + Tisle GC/GEJC anti-PD-(L)1 Naïve
Row 1					

Table 3: Layout for tables by dosage

	Sitra 80 mg	Sitra 120 mg	Sitra Monotherapy	Sitra 80 mg + Tisle	Sitra 120 mg + Tisle	Sitra + Tisle Combination Therapy
Row 1						

6.1. Analysis Sets

The Safety Analysis Set includes all patients who received at least 1 dose of any study drug (any component for the combination therapy). Patients from either Phase 1 or 2 are eligible for inclusion in the Safety Analysis Set.

The Efficacy Evaluable Analysis Set includes all patients who received at least 1 dose of any study drug with measurable disease at baseline per RECIST v1.1 and who had at least 1 evaluable postbaseline tumor assessment unless treatment was discontinued due to clinical disease progression or early death (within 13 weeks of the first dose date). Patients from Phase 1 or 2 are eligible for inclusion in the Efficacy Evaluable Analysis Set.

DLT Evaluable Analysis Set for sitravatinib monotherapy includes patients who received at least 75% of the assigned total dose of sitravatinib for the DLT assessment window. Additionally, patients who had a DLT event will also be considered evaluable. Only patients from Phase 1 are eligible for inclusion in the DLT Evaluable Analysis Set of sitravatinib monotherapy.

DLT Evaluable Analysis Set for sitravatinib and tislelizumab combination includes patients who received at least 75% of the assigned total dose of sitravatinib and ≥ 67% (approximately two-thirds) of the assigned total dose of tislelizumab for the DLT assessment window. Additionally, patients who had a DLT event will also be considered evaluable. Only patients from Phase 1 are eligible for inclusion in the DLT evaluable analysis set of sitravatinib and tislelizumab combination therapy.

The Sitravatinib Pharmacokinetic Analysis Set includes all patients who contributed at least 1 quantifiable PK sample for sitravatinib. The sitravatinib pharmacokinetic analysis set will be used for PK analysis for sitravatinib.

The Tislelizumab Pharmacokinetic Analysis Set includes all patients who contributed at least 1 quantifiable PK sample for tislelizumab. The Tislelizumab Pharmacokinetic Analysis Set will be used for PK analysis for tislelizumab.

The ADA Evaluable Analysis Set includes all patients who received at least 1 dose of tislelizumab and for whom both baseline ADA and at least 1 post-baseline ADA results are available. Patients from either Phase 1 or 2 are eligible for inclusion in the ADA Evaluable Analysis Set.

6.2. Multiplicity Adjustment

Since no formal hypothesis is tested in this study, multiplicity adjustment is not needed.

6.3. Data Analysis General Considerations

6.3.1. Definitions and Computations

Study drugs

Study drugs include tislelizumab and sitravatinib. Tislelizumab (200 mg) will be administered on Day 1 of each 21-day cycle (every 3 weeks). Sitravatinib capsules will be administered orally, once daily continuously for a total daily dose of 120 mg.

Study day

Study day will be calculated in reference to the date of the first dose of study drug for both safety analysis and efficacy analysis. For assessments conducted on or after the date of first dose of study drug, the study day will be calculated as (assessment date – date of first dose of study drug + 1). For assessments conducted before the date of first dose of study drug, study day is calculated as (assessment date – date of first dose of 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 Appendix 1.

Baseline value

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

Study Follow-up Duration

Study follow-up duration (SFD) is defined as the duration from the first dose date to the study discontinuation date (e.g., death, consent withdrawal, lost to follow-up) or to cutoff date if a patient is still ongoing.

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

6.3.2. Conventions

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

- 1 year = 365.25 days. Number of years is calculated as (days/365.25) rounded up to 1 decimal place.
- 1 month = 30.4375 days. Number of months is calculated as (days/30.4375) rounded up to 1 decimal place.
- Duration of image-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 in numerical range, if lab results ≥ x then set as x; if < x, then x/2.
- For by-visit observed data analysis, percentages will be calculated based on the number of patients with non-missing data as the denominator, unless otherwise specified.
- For continuous endpoints, summary statistics will include n, mean, standard deviation, median, Q1, Q3 and range (minimum and maximum). For PK concentration and parameters, geometric mean, and geometric coefficient of variance (CV%) will also be included in the summary while Q1 and Q3 may not be calculated.
- For discrete endpoints, summary statistics will include frequencies and percentages.

6.3.3. Handling of Missing Data

Missing data will not be imputed unless otherwise specified elsewhere in this SAP. Missing dates or partially missing dates will be imputed conservatively for adverse events and prior/concomitant medications/procedures. Specific rules for the handling of missing or partially missing dates for adverse events and prior/concomitant medications/procedures are provided in Appendix 1. By-visit endpoints will be analyzed using observed data unless otherwise specified. For observed data analysis, missing data will not be imputed, and only the observed records will be included.

6.4. Patient Characteristics

6.4.1. Patient Disposition

The number (percentage) of patients who signed informed consent, enrolled in the study, screen failures, screened previously, and reason for screen failure will be summarized by phase in all patients.

The number (percentage) of patients treated, discontinued from the study, discontinued from the treatment (all treatments), reasons for discontinued from the study, reasons for discontinued from the treatment, and the duration of study follow-up will be summarized by phase, indication and dosage in the safety analysis set.

The reasons for patients discontinued from tislelizumab or sitravatinib will be summarized separately by phase in safety analysis set.

Patient data listings of patient disposition will be provided.

6.4.2. Protocol Deviations

Protocol deviation criteria will be established together with its category/term of important and not important. Patients with important protocol deviations will be identified and documented before the database lock. Important protocol deviations will be summarized by phase 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 patient.

6.4.3. Demographic and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized using descriptive statistics in the safety analysis set by indication and by dosage, respectively, including the following variables:

- Age (continuously and by categories [< 65 or ≥ 65 years])
- Sex
- Race
- Ethnicity
- Country
- Weight (kg)
- BMI (kg/m^2)
- ECOG performance status
- PD-L1 score status (TC ≥ 1%, TC < 1%, unknown)
- Smoking status
- Alcohol consumption

6.4.4. Disease History

The number (percentage) of patients reporting a history of disease and characteristics, as recorded on the eCRF, will be summarized by indication and dosage in the safety analysis set.

Disease history of HCC includes the following characteristics.

- BCLC stage at initial diagnosis
- HCC method of first diagnosis
- Histology grade at initial diagnosis
- Time from initial diagnosis to time of diagnosis of metastatic disease/locally advanced disease
- Disease status at study entry
- Time from diagnosis of metastatic disease/locally advanced disease to first dose date
- BCLC staging at study entry
- Child-Pugh classification at study entry
- Known metastatic site at study entry
- Number of metastatic sites at study entry
- Alpha-fetoprotein at baseline

- Macrovascular invasion
- Extrahepatic spread
- HCC etiology

Disease history of Epithelial GC/GEJC includes the following characteristics.

- Primary location
- Disease status at study entry
- Time from initial diagnosis to time of diagnosis of metastatic disease/ locally advanced disease
- Time from diagnosis of metastatic disease/locally advanced disease to first dose date
- Known metastatic site at study entry
- Number of metastatic sites at study entry
- Histology grade at initial diagnosis
- Histology type
- TNM staging at initial diagnosis
- Disease stage at initial diagnosis

The listings of disease history and characteristic with different indications will be provided.

6.4.5. Prior Anticancer Drug Therapies and Surgeries

Prior anticancer drug therapies, prior anticancer surgeries/ procedures with therapeutic intent, and prior radiotherapies will be summarized by indication and by dosage in the safety analysis set. The therapies and surgeries with the same sequence/regimen number are counted as one prior therapy/surgery.

Patient data listings of prior anticancer systemic therapies and prior radiotherapies will be provided in the safety analysis set.

6.4.5.1 Prior Anticancer Drug Therapies

The number (percentage) of patients with any prior anticancer therapy, number of prior lines, type of prior anticancer drug received, duration of last prior anticancer systemic therapy, reasons for discontinuation of last anticancer drug therapy, best overall response to the last anticancer drug therapy, 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.

6.4.5.2 Prior Anticancer Surgeries/ Procedures with Therapeutic Intent

The number (percentage) of patients with any prior anticancer surgery, treatment intent of surgeries, time from last anticancer surgery to first dose, patients with any prior anticancer procedures, prior anticancer procedure name, number of prior anticancer procedures name, number of TACE therapy, treatment intent of procedures, and time from last anticancer procedure to first dose will be summarized in the safety analysis set.

6.4.5.3 Prior Radiotherapies

The number (percentage) of patients with any prior radiotherapy, treatment intent, treatment setting, time from end of last radiotherapy to first dose date, and site irradiated will be summarized in the safety analysis set.

6.4.6. Prior and Concomitant Medications

Prior medications are defined as medications that stopped before the first dose of study drugs. Concomitant medications will be defined as medications that 1) started before the first dose of study drugs and were continuing at the time of the first dose of study drugs, or 2) started on or after the date of the first dose of study drugs 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 Version B3 March 1, 2022. They will be further classified to the appropriate Anatomical Therapeutic Chemical (ATC) code.

The number (percentage) of patients reporting prior and concomitant medications will be summarized by ATC medication class and WHO DD preferred name in the safety analysis set.

6.4.7. Medical History

Medical History will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0. The number (percentage) of patients reporting a history of any medical condition, as recorded on the CRF, will be summarized by System Organ Class and Preferred Term for the Safety Analysis Set.

Patient data listings of medical history will be provided.

6.5. Efficacy Analysis

No formal hypothesis testing is planned for efficacy analysis. Efficacy analyses, except overall survival, will be performed descriptively by indication. Overall survival will be performed descriptively by cohort, i.e., cohort A, B, C, B + C, D.

6.5.1. Primary Efficacy Endpoints

ORR by Investigators

The BOR is the best overall response observed from the date of first dose until disease progression, death, cut-off date, or initiation of post-treatment anticancer therapy, whichever occurs first.

The ORR is defined as the percentage of patients whose BOR is confirmed CR or confirmed PR assessed by investigators per RECIST v1.1. Patients with no post-baseline response assessment (for any reason) will be considered as non-responders. The ORR will be summarized with descriptive statistics by indication and the corresponding two-sided 95% CIs calculated from Clopper-Pearson exact method will be also presented. The primary analysis of ORR is based on Efficacy Evaluable Analysis Set and the sensitivity analysis of ORR is based on the Safety Analysis Set.

ORR based on unconfirmed PR or CR will also be calculated in this study.

6.5.2. Secondary Efficacy Endpoints

Disease Control Rate and Clinical Benefit Rate by Investigators

DCR is defined as the proportion of patients with BOR of CR, PR, and SD in accordance with RECIST v1.1 criteria.

CBR is defined as the proportion of patients with BOR as CR, PR, or SD lasting ≥ 24 weeks assessed by investigator per RECIST v1.1.

DCR assessed and CBR by investigators will be analyzed similarly to ORR.

Progression Free Survival 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. The primary analysis of PFS is based on Safety Analysis Set. The censoring rules for the analysis of PFS are presented in Table 4. Kaplan Meier methodology will be used to estimate median, Q1, and Q3 of PFS, and the event-free rates at 3, 6, 9, and 12 months. 95% CIs for median and other quantiles of PFS 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 M. 1926). Kaplan-Meier curves will be constructed to provide a visual description of the PFS change with time.

Table 4: Censoring Rules for Progression-free Survival Per RECIST Version 1.1

	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	Last adequate radiological assessment before the new anticancer therapy (hypothetical strategy)	Censored
No baseline or post-baseline tumor assessments without death within 13 weeks after first dose	Date of first dose	Censored
No baseline or post-baseline 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

Duration of Response by Investigators

DOR is defined as the time from the first determination of an objective response until the first documentation of PD as assessed by the investigator per RECIST v1.1, or death, whichever comes 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 and Q3, and event-free rates at every 3 months, will be estimated using the Kaplan-Meier method by indication. 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 M. 1926). The analysis of DOR is based on Efficacy Evaluable Analysis Set.

DOR without confirmation by investigator will also be calculated in this study.

Time to Response by Investigators

Time to response (TTR) will be summarized using descriptive statistics, such as mean, median, and standard deviation. Only patients who have achieved objective response by investigators per RECIST v1.1 will be included in the analysis of TTR.

Waterfall plots will be provided for the maximum tumor shrinkage based on target lesion. The maximum tumor shrinkage based on target lesion used in the plots will be listed. The postbaseline nadir will be summarized using descriptive statistics. These analyses will be performed based on RECIST v1.1.

Subgroup Analysis

To assess if the treatment effect is consistent across various subgroups, ORR and DCR by the investigator's review and their 95% CIs will be estimated and plotted within each category of the following subgroups by indication in the Efficacy Evaluable Analysis Set.

For HCC indication, subgroup variables may include, but not limited to,

- Age (< 65 versus ≥ 65)
- Sex (Male versus Female)
- Baseline ECOG (0 versus 1)
- Macrovascular invasion (Yes/No)
- Extrahepatic spread (Yes/No)
- Treatment setting (2L/3L+)
- Disease status (Locally advanced/Metastatic)
- BCLC staging at study entry (B/C)
- Initial dose of Sitravatinib (80mg/120mg)
- Baseline alpha fetoprotein (≤400/>400)

For GC/GEJC indication, subgroup variables may include, but not limited to,

- Age (< 65 versus ≥ 65)
- Sex (Male versus Female)
- Baseline ECOG (0 versus 1)
- Primary tumor location (Stomach/Gastro-esophageal junction)
- Treatment setting (2L/3L+)
- Disease status (Locally advanced/Metastatic)
- Initial dose of Sitravatinib (80mg/120mg)

6.5.3. Exploratory Efficacy Endpoints

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 clinical cutoff date. For patients who are alive by the clinical cutoff date, OS will be censored at the last known alive date. The last known alive date will be defined as either the clinical 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). The patient with imputed death date will be considered as an event for OS analysis.

OS will be analyzed by cohort for patients enrolled in Phase 2 only. The primary analysis of OS is based on Safety Analysis Set.

The distribution of OS, including median, Q1, and Q3, and event-free rates at 3, 6, 9, and 12 months, will be estimated using the Kaplan-Meier method. 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 cohort will be plotted.

6.6. Safety Analysis

All safety analyses will be performed by indication and by dosage 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 AEs, laboratory values, vital signs, and ECG findings.

6.6.1. Extent of Exposure

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

- Duration of exposure (months) for tislelizumab is defined as (last date of exposure - first dose date + 1) / 30.4375. For treatment ongoing patients, use cutoff date as the 'last date of exposure'; for patients treated with tislelizumab and discontinued from treatment, 'last date of exposure' is defined as the earliest date of cutoff date, death date and last dose date + 20.
- Duration of exposure (months) for sitravatinib is defined as (last date of exposure - first dose date + 1) / 30.4375. For treatment ongoing patients, use cutoff date as the 'last date of exposure'; for patients treated with sitravatinib and discontinued from treatment, use last dose date as 'last date 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) is defined as the cumulative dose of the study drug during the treatment period of the study.

- Actual dose intensity (ADI) (mg/cycle) for tislelizumab is defined as the 21 * total cumulative dose (mg) received by a patient / (last dose date prior to cut off date + 21 – first dose date).
- Actual dose intensity (ADI) (mg/day) for sitravatinib is defined as the cumulative dose (mg) received by a patient divided by duration of exposure (days).
- Relative dose intensity (RDI) is defined as the actual dose intensity divided by the planned dose intensity * 100. The planned dose intensity is 200 (mg/cycle) for tislelizumab and 120 (mg/day) or 80 (mg/day) planned dose for sitravatinib.
- Number (%) of patients with dose modifications
- Number (%) of patients with dose reductions and number of dose reductions per patient (sitravatinib only)
- Number (%) of patients with dose interruptions
- Number (%) of patients with dose delay (tislelizumab only)
- Duration of dose interruption (sitravatinib only)

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

6.6.2. Adverse Events

AEs will be graded by the investigators using NCI-CTCAE Version 5.0. The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using MedDRA. AEs will be coded to the MedDRA (Version 25.0 or higher) lowest level term closest to the verbatim term, along with the linked MedDRA Preferred Term (PT) and primary System Organ Class (SOC).

6.6.2.1 Treatment Emergent Adverse Event

A treatment-emergent adverse event (TEAE) is defined as an AE that had onset or increase in severity level date on or after the date of the first dose of study drug up to 30 days after the last dose (any component of combination treatment whichever is last) or the initiation of subsequent anticancer therapy, whichever comes first. Treatment-related TEAEs include those events considered by the investigator to be related to study drug or with a missing assessment of the causal relationship. Summary tables will generally focus on those TEAEs and treatment-related TEAEs. An AE overview table, including the number and percentage of patients with TEAEs, treatment-emergent serious adverse events (SAEs), TEAEs with Grade 3 or above, TEAEs that led to death, TEAEs that led to treatment discontinuation, TEAEs that led to dose modification, treatment-related TEAEs, treatment-related version of any of the above categories will be provided by indication and by dosage.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by SOC, PT, and the worst grade. A patient will be counted only once by the highest severity grade within an SOC and PT, even if the patient experienced more than 1 TEAE within a specific SOC and PT. Summaries of the number (%) of patients with the below types of TEAE will be generated by dosage:

- All TEAEs
  - TEAEs by SOC and PT
  - TEAEs by PT
  - Treatment-related TEAEs by SOC and PT
  - Treatment-related TEAEs by PT
  - TEAEs related to sitravatinib by SOC and PT
  - TEAEs related to tislelizumab by SOC and PT
- Serious TEAEs
  - Serious TEAEs by SOC and PT
  - Serious TEAEs by PT
  - Serious Treatment-related TEAEs by SOC and PT
  - Serious TEAEs related to sitravatinib by SOC and PT
  - Serious TEAEs related to tislelizumab by SOC and PT
- TEAEs with NCI-CTCAE grade ≥3
  - TEAEs with grade ≥3 by SOC and PT
  - TEAEs with grade ≥3 by PT
  - Treatment-related TEAEs with grade ≥ 3 by SOC and PT
  - Treatment-related TEAEs with grade ≥ 3 by PT
  - TEAEs related to sitravatinib with grade ≥ 3 by SOC and PT
  - TEAEs related to tislelizumab with grade ≥ 3 by SOC and PT
- TEAEs leading to death
  - TEAEs leading to death by SOC and PT
  - Treatment-related TEAEs leading to death by SOC and PT
- TEAEs leading to treatment discontinuation by SOC and PT
  - TEAEs leading to treatment discontinuation by SOC and PT
  - Treatment-related TEAEs leading to treatment discontinuation by SOC and PT
  - TEAEs leading to treatment discontinuation of sitravatinib by SOC and PT
  - TEAEs leading to treatment discontinuation of tislelizumab by SOC and PT
- TEAEs leading to treatment modification by SOC and PT
  - TEAEs leading to treatment modification by SOC and PT
  - Treatment-related TEAEs leading to treatment modification by SOC and PT
  - TEAEs leading to treatment modification of sitravatinib by SOC and PT
  - TEAEs leading to treatment modification of tislelizumab by SOC and PT

Summaries of the number (%) of patients with the below types of TEAE will also be generated by indication:

- All TEAEs
  - TEAEs by SOC and PT
  - Treatment-related TEAEs by SOC and PT
- Serious TEAEs
  - Serious TEAEs by SOC and PT
- TEAEs with NCI-CTCAE grade ≥3
  - TEAEs with grade ≥3 by SOC and PT
  - Treatment-related TEAEs with grade ≥ 3 by SOC and PT
- TEAEs leading to death
  - TEAEs leading to death by SOC and PT
  - Treatment-related TEAEs leading to death by SOC and PT
- TEAEs leading to treatment discontinuation by SOC and PT
  - TEAEs leading to treatment discontinuation by SOC and PT
  - Treatment-related TEAEs leading to treatment discontinuation by SOC and PT
- TEAEs leading to treatment modification by SOC and PT
  - TEAEs leading to treatment modification by SOC and PT
  - Treatment-related TEAEs leading to treatment modification by SOC and PT

In addition, Dose-Limiting Toxicity Treatment-Emergent Adverse Events will be summarized by dosage in DLT Evaluable Analysis Set.

Patient data listings of all AEs, treatment-emergent or otherwise will be provided.

6.6.2.2 Immune- Mediated Adverse Event

Immune-mediated adverse events 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 charter. All imAE up to 90 days from the last dose of study drug, regardless of whether the patient starts a new anticancer therapy, will be summarized.

An overall summary table and separate summaries of the following incidence of immune-mediated adverse events will be provided by indication and by dosage:

- imAEs by category and PT
- imAEs by PT
- imAEs ≥ Grade 3 by category and PT
- Serious imAEs by category and PT
- imAEs leading to treatment discontinuation by category and PT

- imAEs leading to tislelizumab discontinuation by category and PT
- imAEs leading to dose modification by category and PT
- imAEs leading to dose modification of tislelizumab by category and PT
- imAEs leading to death by category and PT

Patient data listings of imAEs will be provided.

6.6.2.3 Infusion-related Adverse Event

All AE terms with the wording "Infusion-Related Reactions" (IRRs) or "Infusion Reaction" will be considered as infusion-related AE. Summaries of IRRs incidence by SOC and PT, summaries of IRRs of grade ≥3 or higher by SOC and PT will be provided by indication and by dosage separately

6.6.2.4 Death

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

Patient data listings of deaths will be provided.

6.6.3. Laboratory Values

All the below analysis of laboratory values, vital signs and other safety data will be performed by dosage only.

Laboratory safety tests will be evaluated for selected parameters described in Table 5.

Descriptive summary statistics (n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) for laboratory parameters and their changes from baseline will be summarized by visit.

Laboratories parameters (e.g., hematology, chemistry, and coagulation) are graded in NCI-CTCAE Version 5.0 will be summarized by shifts from baseline NCI-CTCAE grades to maximum post-baseline grades. In the summary of laboratory abnormalities worsened by ≥ 2 Grades (eg, hematology and chemistry), parameters with NCI-CTCAE grading in both high and low directions will be summarized separately. The summary tables will report laboratory assessments up to 30 days of the last dose date.

Laboratory parameters for potential Hy's Law for liver injury and abnormal thyroid function will also be summarized.

Table 5: Clinical Laboratory Assessment

Serum Chemistry	Hematology	Coagulation [a]	Thyroid Function
Alkaline phosphatase	Hematocrit	Prothrombin time or INR	TSH

Alanine aminotransferase	Hemoglobin	aPTT	T3
Aspartate aminotransferase	Platelet counts		T4
Albumin	WBC count		
Total bilirubin	Lymphocyte count		
Direct bilirubin	Neutrophil count		
Blood urea nitrogen or urea			
Potassium			
Sodium			
Corrected calcium [c]			
Creatinine			
Glucose			
Lactate dehydrogenase			
Total protein			
Creatine Kinase (CK) [d]			
CK-MB [d,e]			

Abbreviations: aPTT, activated partial thromboplastin time; CK, creatine kinase; CK-MB, creatine kinase cardiac isoenzyme; INR, International Normalized Ratio; WBC, white blood cell.
[a] Coagulation tests are required at baseline and subsequently as clinically indicated
[b] On routine urinalysis, if urine protein is ≥ 2+ by dipstick, then obtain a 24-hour urine sample for total protein or a random urine sample for total protein and creatinine to determine a protein to creatinine ratio.
[c] If testing for corrected calcium is not feasible at the local laboratory, total calcium may be performed instead.
[d] Patients receiving tislelizumab will receive CK and CK-MB testing. If tislelizumab has been permanently discontinued, CK and CK-MB testing is no longer required. Patients with a history

of cardiological disease receiving sitravatinib monotherapy, either in Cohort A or after discontinuation of tislelizumab, may receive CK and CK-MB testing if clinically indicated.
[e] In the event that CK-MB fractionation is not available, please assess troponin I and/or troponin T instead.

6.6.4. Vital Signs

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

- 140 mmHg to 159 mmHg, 160 mmHg to 179 mmHg, or ≥ 180 mmHg
- > 0, > 20, > 40, or > 60 mmHg maximum increase from baseline

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

- 90 mmHg to 99 mmHg, 100 mmHg to 109 mmHg, or ≥ 110 mmHg
- > 0, > 10, > 20, or > 30 mmHg maximum increase from baseline

6.6.5. 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

6.6.6. Eastern Cooperative Oncology Group (ECOG) Performance Status

A shift table from baseline to worst post-baseline in ECOG Performance Status will be summarized.

6.7. Pharmacokinetic Analysis

The PK concentrations will be determined using plasma (sitravatinib) or serum (tislelizumab)

samples collected at specified time points within a reasonable variation window.

6.7.1. Pharmacokinetic Analysis of Sitravatinib

Serial PK samples will be collected from all patients per cohort after single dose (C1D1) and at steady state (C1D21) in Phase 1. For patients enrolled in Phase 2 samples at predose (within 30 min before administration of sitravatinib) and 6 hours post dose will be collected on Day 1 of Cycles 1, 2, and 5. In the following situations additional PK sample may be collected: when a DLT event or SAE occurs, when a dose reduction happens, or when hepatic impairment status proceeds from mild to moderate in HCC patient cohorts.

Plasma Concentrations will be summarized with descriptive statistics for both serial and sparse PK samples. A value of concentration below the assay quantification limit (BLQ) will be considered zero in the summary and not included in the calculations of geometric mean and geometric coefficient of variation (CV). Concentration versus time will be plotted for patients with serial plasma samples individually and summarized graphically using arithmetic mean (+SD) plots by

cohort for patients, respectively in the linear (ie, original) scale and semi-logarithmic scale. Arithmetic mean concentrations that are BLQ shall be set to zero for plotting on both linear scale but not shown in semi-logarithmic scale. PK parameters will be calculated based on the BeiGene Work Instruction. The PK parameters will be summarized with descriptive statistics for the serial PK samples. If data allows, the PK parameters will include:

- $AUC_{0\text{-}t}$, area under the plasma concentration-time curve from time zero to the last measurable time point
- $AUC_{0\text{-}tau}$, area under the plasma concentration-time curve during dose interval
- $AUC_{0\text{-}inf}$, area under the plasma concentration-time curve from time zero to infinity
- C_{max}, maximum plasma concentration
- CL/F, clearance after oral administration
- T_{max}, time to maximum plasma concentration
- $t_{1/2}$, terminal elimination half-life
- V_z/F, the terminal volume of distribution after oral administration
- R_o, observed accumulation ratio determined by the ratios of parameters ($AUC_{0\text{-}tau}$ and C_{max}) at steady state and single dose.

Accumulation ratios for selected PK parameters (AUC and C_{max}) will be estimated by geometric mean ratios of the parameters at steady state (ss, [Cycle 1 Day 21]) and single dose (sd, [Cycle 1 Day 1]) (i.e., $AUC_{0\text{-}tau,ss}$ versus $AUC_{0\text{-}tau,sd}$ for AUC and $C_{max,ss}$ versus $C_{max,sd}$ for plasma concentration) in linear mixed effect models. The linear mixed effect model for each selected parameter will include the natural logarithmic-transformed PK parameter as the dependent variable, fixed effect of Day (steady state vs single dose) and random effect of patient as independent variables. Each accumulation ratio will be estimated by applying the exponential function on the difference of least square (LS) means of $\log(PK_{ss})$ and $\log(PK_{sd})$. Similarly the 95% CI for an accumulation ratio will be obtained by applying the exponential function on the 95% CI for the mean of $\log(PK_{ss})$ - $\log(PK_{sd})$. For each of the selected PK parameters, the intrasubject CV will be calculate by $\sqrt{e^{MSE} - 1}$ where MSE is the expected mean square error for within patient variability obtained from the linear mixed effect model. Inter-subject CV will be calculated as $\sqrt{e^{S^2} - 1}$ where S^2 is the estimate of variance for the random effect of patient. For each selected parameter, only patients with valid values at single dose and steady state will be included for analyses of accumulation, intra-subject CV and inter-subject CV.

6.7.2. Pharmacokinetic Analysis of Tislelizumab

In Phase 1 and Phase 2, predose (within 30 min before starting tislelizumab infusion) samples should be collected on Day 1 of Cycles 1, 2, 5, 9, and 17 (if achieved); two postdose (within 30 min after the end of tislelizumab infusion) samples should be collected at C1D1 and C5D1; and an additional blood PK sample should be collected at the EOT Visit. Should a patient present with DLT event or ≥ Grade 3 or above irAE, additional blood PK samples may be taken to determine the serum concentration of tislelizumab. Serum Concentrations will be summarized with descriptive statistics.

6.8. Immunogenicity Analysis

ADA samples for tislelizumab should be collected Day 1 (Predose of tislelizumab, -30 min) of Cycles 1, 2, 5, 9 and 17, and at the EOT Visit. All samples should be drawn at the same time as the PK blood collection for pre-dose of tislelizumab.

The scope of 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 or additional parameters may be added.

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 patient: Number of patients with reportable non-missing baseline result and at least one reportable sample taken after Tislelizumab 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 patients. Synonymous with “ADA Incidence”.
- Treatment-induced ADA: ADA-evaluable patients that were ADA-negative at baseline and ADA-positive following administration of biologic product.
- Treatment-boosted ADA: Baseline-positive ADA-evaluable patient with significant increases (4-fold or higher) in ADA titer after Tislelizumab administration. Baseline-positive ADA-evaluable patient is an ADA-evaluable patient with positive ADA result.
- 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.
- 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 ANALYSIS

No interim analysis is planned.

8. CHANGES IN THE PLANNED ANALYSIS

Table 6 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 6: Statistical Analysis Plan Changes

SAP version	Approval date	Change made from	Rationale of the change	Description of the change
1.0	This version	Protocol V4.0	To clarify the definition of the efficacy evaluable analysis set.	1) Change the "disease progression" from the definition of efficacy evaluable analysis set in the protocol into "clinical disease progression" in the SAP. 2) Change the "death before tumor assessment" from the definition of efficacy evaluable analysis set in the protocol into "early death (within 13 weeks of the first dose date)" in the SAP
1.0	This version	Protocol V4.0	To clarify the pharmacokinetic analysis set of different study drugs.	Split the Pharmacokinetic Analysis Set in protocol into Sitravatinib Pharmacokinetic Analysis Set and Tislelizumab Pharmacokinetic Analysis Set in the SAP.
1.0	This version	Protocol V4.0	To align with BeiGene's current standard	The definition of TEAE is different between protocol and SAP. In the protocol, "TEAE classification also applies to irAEs recorded up to 90 days after the last dose of tislelizumab, regardless of whether the patient starts a new anticancer therapy." In this SAP, "If an imAE occurs outside of the above-mentioned TEAE window, it will not be classified as a TEAE". The update of TEAE window streamlines the TEAE derivation so all TEAEs can be identified programmatically instead of relying on the manual medically review of imAE.
1.0	This version	Protocol V4.0	To align with BeiGene's current standard	Change the name of immune-related adverse events (irAEs) into immune-mediated AEs (imAEs).

9. REFERENCES

BeiGene Work Instruction. Best Practice Guidance: Non-Compartmental Pharmacokinetic Data_Analysis for Clinical Studies. Version 1.0, December 2020.

Brookmeyer, Ron, and John Crowley. 1982. 'A Confidence Interval for the Median Survival Time'. *Biometrics* 38 (1): 29–41. https://doi.org/10.2307/2530286.

CTCAE V5.0, November 27, 2017. *Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.* Washington, DC, USA: Department of Health and Human Services, National Institutes of Health, National Cancer Institute.

Eisenhauer, E.A., P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, et al. 2009. 'New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (Version 1.1)'. *European Journal of Cancer* 45 (2): 228–47. https://doi.org/10.1016/j.ejca.2008.10.026.

Greenwood M. The Natural Duration of Cancer. Reports on Public health and medical subjects. 1926; 33:1-26.

APPENDIX 1. IMPUTATION OF MISSING OR PARTIALLY MISSING DATES

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

1.1 Prior/Concomitant Medications/Procedures

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 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 of the month
- If the imputed start date > death date, then set to death date

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 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.

1.2 Adverse Events

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

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

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

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

1.3 Disease history and prior therapy (Drug, surgery/procedure, radiotherapy)

For prior therapy, impute end date first.

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

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

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

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

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 date of a disease history is partially missing, impute as follows:

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

If diagnosis date of metastatic disease/locally advanced is partially missing, impute as follows:

- If both month and day are missing, then set to January 01
- If only day is missing, then set to the first of the month
- If the imputed date > first dose date, then set to first dose date – 1
- If the imputed date < (imputed) date of initial diagnosis date, then set to initial diagnosis date.

If the date of response to prior therapy is partially missing, impute as follows:

- If both month and day are missing, then set to January 01

- If only day is missing, then set to the first of the month
- If the imputed date > first dose date, then set to first dose date – 1

If the imputed date < the start date of prior therapy, then set to the start date of prior therapy +1.

1.4 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, data cutoff date, study discontinuation date, start date of the next subsequent therapy), then set it as min (death date, data cutoff date, study discontinuation 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, data cutoff date, study discontinuation date, start date of the next subsequent therapy), then set it as min (death date, data cutoff date, study discontinuation 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. RULES FOR IDENTIFYING MISSING TUMOR ASSESSMENTS

Identifying two missing tumor assessments

1) Input scheduled TA visit list
    a. (6wk-12wk-18wk-24wk-30wk-36wk-42wk-48wk) for this study with TA as every 6 weeks for the first 12 months (52 weeks), then every 9 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) as –LPTADT_WK. It can be achieved programmatically by following the classification rule (e.g. defining thresholds) depicted in Table 7 below. (The team can consider mapping all tumor visits if the scheduled visits are uncleaned or questionable)
    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 (assuming 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

Table 7 shows how to assign unscheduled TA to a schedule visit. 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). For example, if LPTADT is Week 44 for an unscheduled visit, it will be mapped to Week 42 TA since it is within the threshold for Week 42. Assuming it is SD and the subsequent TA of the patient is PD after Week 58, PFS will be censored at LPTADT (Week 44); had the PD occurred prior to Week 58, it would be counted as an PFS event.

Table 7: Example of scheduled tumor assessments with time window

Weeks	Scheduled week -1	Scheduled week	Scheduled week+1	Threshold
Baseline		Baseline		
Every 6 weeks for the first 52 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 52
Every 9 weeks thereafter	Week 56	**Week 57**	Week 58	Week 61
	Week 65	Week 66	Week 67	Week 70
	Week 74	Week 75	Week 76	…