16.1.9 DOCUMENTATION OF STATISTICAL METHODS

BeiGene

STATISTICAL ANALYSIS PLAN

Study Protocol Number:	BGB-A317-212
Study Protocol Title:	A Multicenter, Open-Label, Phase 2 Study to Evaluate the Efficacy and Safety of Tislelizumab in Combination with Lenvatinib in Patients with Selected Solid Tumors
Date:	09 Nov 2023
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SIGNATURE PAGE

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Antidrug Antibody
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
CI	Confidence Interval
CR	Complete Response
CT	Computed Tomography
DCR	Disease Control Rate
DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic Acid
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
imAE	immune-mediated Adverse Event
GC	Gastric Cancer
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MSI	Microsatellite Instability
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NSCLC	Non-Small Cell Lung Cancer
ORR	Overall Response Rate

Abbreviation	Definition
OS	Overall Survival
PD	Progressive Disease
PD-1	Programmed cell Death protein-1
PD-L1	Programmed cell Death Ligand-1
PFS	Progression-Free Survival
PK	Pharmacokinetic
PR	Partial Response
PT	Preferred Term
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCCHN	Squamous Cell Carcinoma of Head and Neck
SD	Stable Disease
SMC	Safety Monitoring Committee
SOC	System Organ Class
TA	Tumor Assessment
TEAE	Treatment-Emergent Adverse Event
TMB	Tumor Mutational Burden
TTR	Time To Response
UC	Urothelial Cancer
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-A317-212: a multicenter, open-label, phase 2 study to evaluate the efficacy and safety of Tislelizumab in combination with Lenvatinib in patients with selected solid tumors. This SAP is based on BGB-A317-212 Protocol Amendment 2.0, dated on November 03, 2022. The focus of this SAP is for the primary and final analysis specified in the study protocol.

2. STUDY OVERVIEW

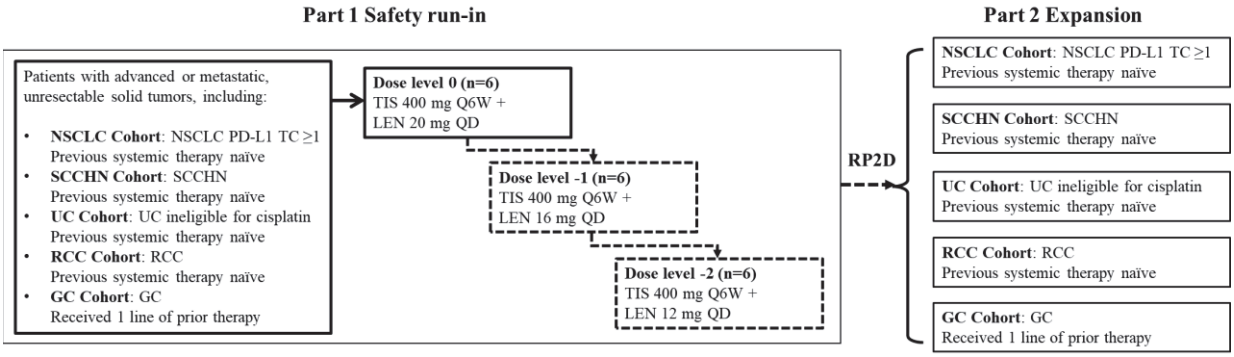
2.1. Study Design

This is an open-label, multicenter, Phase 2 study to evaluate the safety and preliminary anticancer activity of Tislelizumab in combination with Lenvatinib in Chinese patients with locally advanced or metastatic tumors including PD-L1 positive non-small cell lung cancer (NSCLC), squamous cell carcinoma of head and neck (SCCHN), urothelial cancer (UC), renal cell carcinoma (RCC) and gastric cancer (GC). This study includes 2 parts, Part 1 as safety run-in stage and Part 2 to assess the efficacy and safety of Tislelizumab in combination with Lenvatinib (Figure 1).

Six patients will receive Lenvatinib 20 mg orally once daily as starting dose in combination with Tislelizumab 400 mg intravenously once every 6 weeks, and up to 18 patients will be dosed if lower dose(s) of Lenvatinib in combination with Tislelizumab need to be assessed to determine RP2D in Part 1. The SMC will evaluate the safety of the combination therapy when the first 6 DLT-evaluable patients have completed the first 28 days of treatment. Once the SMC confirms that the combination therapy is tolerable to proceed, the current dose will be recommended by SMC as RP2D for Part 2, and enrollment for Part 2 will begin at this dose. Patients enrolled in Part 1 at the RP2D will be counted towards Part 2 by the diagnosed tumor type, and total patient number including Part 1 and Part 2 will be approximately 30 at RP2D in cohort of each tumor type. There will be a total of 5 cohorts in the study as NSCLC, SCCHN, UC, RCC and GC, respectively. Patients will receive the study drug(s) until occurrence of PD, starts new anticancer therapy, lost to follow-up, unacceptable toxicity, death, withdrawal of consent, or study termination by sponsor.

All patients will be closely monitored for adverse events (AEs) throughout the study and for ≥ up to 30 days after the last dose of study drug(s). AEs will be graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0.

Figure 1: Study Schema



Abbreviations: TIS, Tislelizumab; LEN, Lenvatinib; NSCLC, non-small cell lung cancer; SCCHN, squamous cell carcinoma of head and neck; UC, urothelial cancer; RCC, renal cell carcinoma; GC, gastric cancer; PD-L1, programmed cell death ligand-1, QD, once daily; Q6W, once every 6 weeks.

2.2. Study Assessments

Tumor assessments will be performed by the investigators based on RECIST v1.1. All scans for tumor assessments performed during the study should be archived in accordance with the standard local practice. Tumor imaging at Screening must be performed within 28 days before first dose of study drugs (Cycle 1 Day 1).

Tumor assessments will be carried out every 9 weeks (±7 days) (counting from C1D1) in the first year (54 weeks), then every 12 (±7 days) weeks thereafter until disease progression, begins subsequent anticancer therapy, loss to follow-up, withdrawal of consent, death, or until study termination, whichever occurs first.

Patients will be evaluated for any AEs and SAEs occurring until up to 30 days after the last dose of study drug(s) (all severity grades, per NCI-CTCAE v.5.0) or initiation of 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 subsequent anticancer therapy. All AEs and SAEs will be followed until resolution, the condition stabilizes or is considered chronic, the AE or SAE is otherwise explained, the patient is lost to follow-up, or the patient withdraws consent. All SAEs considered related to the study drug(s) that are brought to the attention of the investigator should be reported regardless of time since the last dose of treatment.

3. STUDY OBJECTIVES

3.1. Primary Objective

Part 1 (Safety run-in)

- To assess the safety and determine RP2D) of Lenvatinib (20 mg or other dose once a day [QD]) in combination with Tislelizumab (intravenous [IV], 400 mg every six weeks [Q6W]) in patients with advanced solid tumors.

Part 2 (Expansion)

- To assess the overall response rate (ORR) of Tislelizumab (IV, 400 mg Q6W) in combination with Lenvatinib in patients with selected advanced tumors.

3.2. Secondary Objective

Part 2 (Expansion)

- To evaluate the preliminary anticancer activity of Tislelizumab (IV, 400 mg Q6W) in combination with Lenvatinib using progression-free survival (PFS), duration of response (DOR), disease control rate (DCR), and overall survival (OS).
- To characterize the safety of Tislelizumab (IV, 400 mg Q6W) in combination with Lenvatinib.

3.3. Exploratory Objective

Part 2 (Expansion)

- To explore potential biomarkers that may correlate with clinical responses/resistance to Tislelizumab in combination with Lenvatinib.
- To characterize the pharmacokinetics and immunogenicity of Tislelizumab when given in combination with Lenvatinib.

4. STUDY ENDPOINTS

4.1. Primary Endpoint(s)

Part 1 (Safety run-in)

- Adverse events (AEs) and serious adverse events (SAEs) as characterized by type, frequency, severity (as graded by NCI-CTCAE Version 5.0), timing, seriousness, and relationship to study drug(s); physical examinations, electrocardiograms (ECGs), and laboratory assessments as needed; and AEs meeting protocol-defined DLT criteria.

Part 2 (Expansion)

- ORR, as assessed using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 by investigator.

4.2. Secondary Endpoints

Part 2 (Expansion)

- PFS, DOR, DCR, as assessed using RECIST Version 1.1 by investigator, and OS.
- AEs and SAEs as characterized by type, frequency, severity (as graded by NCI-CTCAE Version 5.0), timing, seriousness, and relationship to study drug(s); physical examinations, ECGs, and laboratory assessments as needed.

4.3. Exploratory Endpoints

Part 2 (Expansion)

- Potential biomarker of PD- L1 expression and its association with response to Tislelizumab in combination with Lenvatinib.
- Serum concentrations of tislelizumab and the incidence of ADA.

5. SAMPLE SIZE CONSIDERATIONS

The study plans to enroll approximately 70 patients:

- Part 1 (Safety run-in): Approximately 6 to 18 patients with 5 prespecified tumor types
- Part 2 (Expansion): To enroll additional patients at RP2D up to approximately 30 patients in the prespecified tumor type

Three cohorts were closed prior to planned enrollment due to emerging data (NSCLC and UC cohorts) and changes to first-line standard of care (GC cohort). In the SCCHN and RCC cohorts, approximately 30 patients per cohort will be enrolled to evaluate the preliminary efficacy. No formal hypothesis testing will be performed in the efficacy evaluation.

6. STATISTICAL METHODS

6.1. Analysis Sets

The Safety Analysis Set includes all patients who received ≥ 1 dose of study drug(s). This will be the analysis set for the safety and efficacy analyses.

The Evaluable Analysis Set includes all patients who received ≥ 1 dose of study drug(s), have evaluable disease at baseline, and have ≥ 1 evaluable postbaseline tumor response assessment unless any clinical PD or death occurred before the first postbaseline tumor assessment.

The DLT Evaluable Analysis Set includes patients enrolled during safety run-in stage who

- Received ≥ 75% of scheduled Lenvatinib and ≥ 67% (approximately two-thirds) of scheduled dose intensity of Tislelizumab administration during the DLT assessment window, remained on study during the DLT observation period, and had sufficient safety evaluation OR
- Experienced a DLT within the DLT observation period.

The PK Analysis Set includes all patients who received ≥ 1 dose of Tislelizumab and have ≥ 1 quantifiable postbaseline PK data.

The ADA Analysis Set includes all patients who received ≥ 1 dose of study drug(s) and have a baseline and at least 1 postbaseline ADA result.

6.2. Multiplicity Adjustment

Not applicable.

6.3. Data Analysis General Considerations

6.3.1. Definitions and Computations

Study drugs include Tislelizumab in combination with Lenvatinib.

Reference date: Reference date is defined as the date of the first dose of study drug and will appear in every listing where an assessment date or event date appears.

Study Day: Study day will be calculated in reference to the date of the first dose of study drug. For assessments conducted on or after the date of the first dose, the study day will be calculated as (assessment date – the first dose date + 1). For assessments conducted before the date of the first dose, study day is calculated as (assessment date – the first dose date). There is no study day

0. In the situation where the event date is partial or missing, the date will appear partial or missing in the listings. Study day and any corresponding durations will be presented based on the imputations specified in Appendix 1.

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

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 significant digit.
- 1 month = 30.4375 days. Number of months is calculated as (days/30.4375) rounded up to 1 significant digit.
- Age will be calculated as the integer part of (date of informed consent – date of birth + 1)/365.25.
- 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 as in numerical range, if lab results >= x or >x then set as x; if < x or <=x, then x/2.
- For by-visit observed data analyses, percentages will be calculated based on the number of patients with non-missing data as the denominator, unless otherwise specified.
- For continuous endpoints, summary statistics will include n, mean, standard deviation, median, Q1, Q3 and range (minimum and maximum).
- For discrete endpoints, summary statistics will include frequencies and percentages.

6.3.3. 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, disease history and prior therapy, prior/concomitant medications/procedures and subsequent anticancer therapy. Specific rules for the handling of missing or partially missing dates are provided in Appendix 1.

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

6.4. Patient Characteristics

6.4.1. Patient Disposition

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

6.4.2. Protocol Deviations

Important protocol deviation criteria will be established, and patients with important protocol deviations will be identified and documented. Important protocol deviations will be summarized for all patients in the safety analysis set. They will also be listed by each category. Deviation categories are not mutually exclusive. Multiple deviations within the same category are counted once per 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, including but not limited to the following variables:

- Age (continuously and by categories [≤65 or >65 years])
- Sex
- Race
- Weight
- ECOG performance status at baseline

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 in the safety analysis set. Disease characteristics include disease stage at initial diagnosis, patients with metastatic disease at study entry, time from initial diagnosis to first dose date, time from initial diagnosis of metastatic disease to first dose date, time from initial diagnosis of locally advanced disease to first dose date, histology/cytology, histologic grade.

6.4.5. Prior Anticancer Drug Therapies and Surgeries

Prior anti-cancer drug therapies, prior anti-cancer radiotherapy, and prior anti-cancer surgeries will be summarized in the safety analysis set. The variables include number of patients with any prior anti-cancer drug therapy, number of prior lines, reason(s) 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, treatment setting for prior anti-cancer drug therapies and number of patients with any prior anticancer surgery, time from last anticancer surgery to first dose date for prior surgeries. The therapies and surgeries with the same sequence/regimen number are counted as one prior therapy/surgery.

6.4.6. Prior and Concomitant Medications

Prior medications are defined as medications that stopped before the first dose of study drug. Concomitant medication is defined as medications that received (started before, on or after the date of the first dose of the treatment) during study treatment period from initialization of treatment up to 30 days after treatment, regardless of whether to receive any subsequent anti-cancer therapy.

Prior and concomitant medications will be coded using the version of World Health Organization Drug Dictionary (WHO DD) drug codes version for the study at the time of database lock. 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 for the study at the time of database lock. The number (percentage) of patients reporting a history of any medical condition, as recorded on the CRF, will be summarized by system organ class and preferred term in the safety analysis set.

6.4.8. Subsequent Anti-cancer Therapy

Subsequent anti-cancer therapy is defined as the anti-cancer therapy started after the last dose date of study treatment. A summary of number (percentage) of patients who receive subsequent anti-cancer therapy in procedure/surgery or radiotherapy or systematic anti-cancer therapy will be provided based on safety analysis set. A listing of subsequent anti-cancer therapy will be provided.

6.5. Efficacy Analysis

Primary and/or secondary efficacy endpoints will be based on investigators' tumor assessments per RECIST Version 1.1.

6.5.1. Primary Efficacy Endpoint(s)

The primary analysis is planned in around 9 months after the last patient received the first dose of study drug. The investigator assessment will be used for the analysis. Patients without postbaseline tumor assessment will be considered as non-responders. The number and proportion of patients who achieve the objective response (CR/PR) will be summarized. Associated 2-sided 95% Clopper-Pearson confidence interval (CI) of ORR (defined as the proportion of patients who had CR or PR) will be calculated by cohort based on Safety Analysis Set and Evaluable Analysis Set.

Best Overall Response (BOR) which is defined as the best response recorded from the start of the study drug until data cut or start of new antineoplastic treatment. Patients with no post-baseline response assessment (due to whatever reason) will be considered non-responders for BOR. The number and proportion for each of the response categories (complete response [CR], partial response [PR], stable disease [SD], and progressive disease [PD]) will be presented.

A swimmer plot of time on treatment (ie, duration of exposure), with indicators for the start and end of each response episode classified by CR or PR, will also be provided for the cohorts with at least 10 patients. The patients will be ordered by the duration of exposure. Patients with the longest duration will be presented at the top of the plot.

Forest plot for selected cohorts in the expansion stage with sufficient sample size will be provided.

6.5.2. Secondary Efficacy Endpoints

Progression Free Survival (PFS)

PFS is defined as the time from the date of the first dose of study drugs to the date of the first documentation of PD or death, whichever occurs first. Kaplan Meier methodology will be used to estimate median PFS, Q1 and Q3 of PFS, and the event-free rates at selected timepoints, e.g. 3, 6, 9, and 12 months based on Safety Analysis Set. 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, 1926). Kaplan Meier curves will be constructed to provide a visual description of the PFS change with time for the cohorts with at least 10 patients. PFS censoring rule will follow

the US FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2018). The censoring rules for the primary analysis of PFS are presented in **Error! Reference source not found.**.

Table 1. 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	Censored
New anticancer therapy started	Last adequate disease assessment before the new anticancer therapy	Censored
No baseline or post-baseline tumor assessments without death within 19 weeks after the first dose after the first dose	Date of the first dose	Censored
No baseline or post-baseline tumor assessments and died within 19 weeks after the first dose	Date of death	Event
Death or progression after more than one missed visit	Date of last adequate radiologic assessment before missed tumor assessments	Censored
Progression documented at or between scheduled visits	Date of first radiologic PD assessment	Event
Death before first PD assessment	Date of death	Event

Duration of Response (DOR)

Duration of response analysis will only include responders. The censoring rule for DOR will follow the PFS censoring rule. Kaplan Meier methodology will be used to estimate the median duration, and the 95% confidence interval for the duration of response will be provided based on Evaluable Analysis Set.

Disease control rate (DCR), defined as the proportion of patients with best overall response of a CR, PR, or SD, will be analyzed using methods similar to those described for ORR based on the Safety Analysis Set and Evaluable Analysis Set.

Waterfall plots will be provided for the maximum tumor shrinkage based on target lesion(s). The maximum tumor shrinkage based on target lesion(s) used in the plots will be listed for the cohorts with at least 10 patients.

Overall survival (OS)

OS, defined as the time from the date of the first dose of study drugs to death due to any cause, will be analyzed in the Safety Analysis Set using methods similar to those described for PFS, except for censoring rules. For OS, patients will be censored either at the date that the patient was last known to be alive or the date of data cutoff, whichever comes earlier, in the absence of death. OS rates at specific timepoints will be calculated based on the Kaplan-Meier method.

Time to Response (TTR) will be analyzed using sample statistics such as mean, median and standard deviation in the responders.

6.6. Safety Analyses

All safety analyses will be performed by cohorts based on safety analysis set except for analysis of DLT which is only applicable to patients in DLT Evaluable 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 (hematology, clinical chemistry, coagulation, and urinalysis), vital signs, ECG findings and physical examination.

6.6.1. Extent of Exposure

The following measures of the extent of exposure will be summarized for Tislelizumab and Lenvatinib (One cycle is defined as 42 days for Tislelizumab):

- Duration of exposure (months) is defined as last date of exposure – first dose date + 1:

  For Tislelizumab Q6W, it is calculated as (min (cutoff date, death date, last dose date + 41) – first dose date + 1)/30.4375.

  For Lenvatinib QD, it is calculated as (min (cutoff date, death date, last dose date) – first dose date + 1)/30.4375.

- Number of treatment cycles received: defined as the total number of treatment cycles in which at least one dose of the study drug is administered.

- Total dose received per patient (mg): defined as the cumulative dose of the study drug during the treatment period of the study.
- Actual dose intensity (mg/cycle): defined as the total dose received by a patient divided by the duration of exposure.
  For Tislelizumab, it will be calculated as

$$\frac{\text{total cumulative dose} \times 42}{\text{last dose date up to cutoff date} + 42 - \text{first dose date}}$$

  For Lenvatinib (mg/day), it will be calculated as

$$\frac{\text{cumulative dose}}{\text{last dose date up to cutoff date} + 1 - \text{first dose date}}$$

- Relative dose intensity (%): defined as the ratio of the actual dose intensity and the planned dose intensity. Planned dose intensity is defined as the planned dose on study day 1 by a patient divided by the duration of exposure.
- Number (%) of patients with dose delay
- Number (%) of patients with dose missing
- Number (%) of patients with dose interruptions
- Number (%) of patients with dose modifications
- Reasons for dose delay
- Reasons for dose interruptions
- Reasons for dose modifications

6.6.2. Adverse Events

AEs will be graded by the investigators using CTCAE version 5.0. The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using MedDRA. Adverse events will be coded to the MedDRA (Version 26.1 or above) lowest level term closest to the verbatim term, along with the linked MedDRA preferred term (PT) and primary system organ class (SOC).

A treatment-emergent adverse event (TEAE) is defined as an AE that had onset or increase in severity level date on or after the date of the first dose of study drug through 30 days after the last dose (permanent discontinuation of study drug) or the initiation of new anti-cancer therapy, whichever is earlier. Summary tables will generally focus on those AEs that were treatment-emergent (TE). All AEs, treatment-emergent or otherwise, will be presented in patient data

listings.

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 treatment modification, treatment-related TEAEs, treatment-related TEAEs serious adverse events (SAEs), treatment-related TEAEs with Grade 3 or above, treatment-related TEAEs that led to death, treatment-related TEAEs that led to treatment discontinuation, treatment-related TEAEs that led to treatment modification will be provided. Treatment-related AEs include those events considered by the investigator to be related to study drug or with a missing assessment of the causal relationship.

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

Immune-mediated adverse events (imAE) will be reported until 90 days after the last dose of tislelizumab regardless of initiation of a new anti-cancer therapy. All imAE (serious, grade>=3, leading to death, leading to treatment discontinuation, leading to treatment modification) will be summarized reported separately. ImAE outcome, time to onset, and duration by category will also be summarized in table.

Infusion related AE also will be summarized and reported.

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

6.6.3. Laboratory Values

Laboratory safety tests will be evaluated for selected parameters described in Table 2. Parameters selected from Table 2 will be summarized as appropriate.

Laboratory parameters (*e.g.* ALP, ALT, AST, total bilirubin, albumin, hemoglobin, platelet counts, WBC count, neutrophil and lymphocyte) that are graded in NCI CTCAE Version 5.0 or higher will be summarized by shifts from baseline CTCAE grades to maximum post-baseline

grades. In the summary of laboratory parameters by CTCAE grade, parameters with CTCAE grading in both high and low directions will be summarized separately.

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

Patient data listings of selected list of lab parameters will be provided as appropriate.

Table 2: Serum Chemistry and Hematology Laboratory Tests

Serum Chemistry	Hematology
Alkaline Phosphatase (ALP)	Red Blood Cell Count
Alanine Aminotransferase (ALT)	Hematocrit
Aspartate Aminotransferase (AST)	Hemoglobin
Albumin	Platelet Count
Total Bilirubin	White Blood Cell Count
Direct Bilirubin	Lymphocytes Count
Blood Urea Nitrogen or Urea	Neutrophils Count
Amylase	
Lipase	
Potassium	
Sodium	
Total Calcium	
Creatinine	
Glucose	
Lactate Dehydrogenase (LDH)	
Total Protein	
CK	
CK-MB	
Magnesium	

6.6.4. Vital Signs

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

Shift tables assessing the toxicity grade at baseline versus worst toxicity recorded post-baseline will be presented.

6.6.5. Eastern Cooperative Oncology Group (ECOG) Performance Status

A shift table from baseline to worst post-baseline in ECOG performance status will be summarized. ECOG status will be summarized by visit.

6.7. Pharmacokinetic Analyses

Blood samples will be collected for Tislelizumab PK evaluation at predose and postdose; the serum concentration data will be tabulated and summarized by the visit/cycle at which these samples are collected. Descriptive statistics will include mean, median, range, and standard deviation as appropriate.

6.8. Immunogenicity Analyses

The immunogenicity results for Tislelizumab will be summarized using descriptive statistics by the number and percentage of patients who develop detectable ADAs. The incidence of positive ADAs and neutralizing ADAs will be reported for evaluable patients. The effect of immunogenicity on PK, efficacy, and safety may be evaluated if data allow and reported separately from the main clinical study report.

6.9. Other Analyses

Biomarker of PD- L1 expression in squamous cell carcinoma of the head and neck (SCCHN), and its association with response to Tislelizumab in combination with Lenvatinib will be analyzed.

7. INTERIM ANALYSES

No formal interim analysis will be conducted. Summaries of efficacy and safety data may be generated to inform subsequent clinical development planning.

8. CHANGES IN THE PLANNED ANALYSIS

Not applicable.

9. REFERENCES

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics. 1982;38:29-41.

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

US Food and Drug Administration Center for Drug Evaluation Research (CDER) and Center for Biologics Evaluation and Research. FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. 2018.

APPENDIX 1. IMPUTATION OF MISSING OR PARTIALLY MISSING DATES

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

1. Impute partial dates for concomitant medication

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

If 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.

2. Impute partial dates for adverse events

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

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

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

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

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

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

with AE end date as final imputed AE start date

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

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

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

Impute end date first. If end date is partially missing, impute as follows:

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

If start date is partially missing, impute as follows:

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

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

4. Impute partial dates for subsequent anti-cancer therapy as collected in the post-treatment page (same rule applies to safety and efficacy flag)

If start date of subsequent anti-cancer therapy is partially missing, impute as follows:

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

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

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

The (imputed) stop date must be after or equal to the (imputed)start date

If year of the start date/stop date is missing, do not impute.

Note: if the imputed subsequent anti-cancer therapy date collected from CRF “post-treatment discontinuation anti-cancer systemic therapy” or “post-treatment discontinuation anti-cancer procedure” page is before the last dosing date, send data query.